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Signed Stephen Hordley

Dated 7 August 2003

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Patents Form 1/77

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14SEP02 E748055-3 D02934
P01/7700 0.00-0221246.2

Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

The Patent Office

Cardiff Road
Newport
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1. Your reference — 100828-1

2. Patent application number *(The Patent Office will fill in this part)* — 0221246.2 — 13 SEP 2002

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

AstraZeneca AB
S-151 85 Sodertalje
Sweden

Patents ADP number *(if you know it)* — 78224800 3

If the applicant is a corporate body, give the country/state of its incorporation — Sweden

4. Title of the invention

COMPOUNDS

5. Name of your agent *(if you have one)*

Hazel Potts

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

AstraZeneca UK Limited
Global Intellectual Property
Mereside, Alderley Park
Macclesfield
Cheshire SK10 4TG

Patents ADP number *(if you know it)* — 78224710 02

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing *(day / month / year)*

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:*

a) any applicant named in part 3 is not an inventor, or
b) there is an inventor who is not named as an applicant, or
c) any named applicant is a corporate body.
See note (d))

ents Form 1/77

9. Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document

Continuation sheets of this form	
Description	57
Claim(s)	9
Abstract	
Drawing(s)	

10. If you are also filing any of the following, state how many against each item.

Priority documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patents Form 9/77)*	
Request for substantive examination *(Patents Form 10/77)*	
Any other documents *(please specify)*	

11. I/We request the grant of a patent on the basis of this application.

Signature Authorised Signatory Date 12/09/2002

12. Name and daytime telephone number of person to contact in the United Kingdom

Jennifer C Bennett - 01625 230148

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Notes

a) If you need help to fill in this form or you have any questions, please contact the Patent Office on 0645 500505.

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COMPOUNDS

The present invention relates to compounds useful in the inhibition of metalloproteinases and in particular to pharmaceutical compositions comprising these, as well as their use.

The compounds of this invention are inhibitors of one or more metalloproteinase enzymes and are particularly effective as inhibitors of TNF-α (Tumour Necrosis Factor-α) production. Metalloproteinases are a superfamily of proteinases (enzymes) whose numbers in recent years have increased dramatically. Based on structural and functional considerations these enzymes have been classified into families and subfamilies as described in N.M. Hooper (1994) FEBS Letters 354:1-6. Examples of metalloproteinases include the matrix metalloproteinases (MMP) such as the collagenases (MMP1, MMP8, MMP13), the gelatinases (MMP2, MMP9), the stromelysins (MMP3, MMP10, MMP11), matrilysin (MMP7), metalloelastase (MMP12), enamelysin (MMP19), the MT-MMPs (MMP14, MMP15, MMP16, MMP17); the reprolysin or adamalysin or MDC family which includes the secretases and sheddases such as TNF-α converting enzymes (ADAM10 and TACE); the ADAM-TS family (for example ADAM-TS1 and ADAM-TS4); the astacin family which include enzymes such as procollagen processing proteinase (PCP); and other metalloproteinases such as the endothelin converting enzyme family and the angiotensin converting enzyme family.

Metalloproteinases are believed to be important in a plethora of physiological disease processes that involve tissue remodelling such as embryonic development, bone formation and uterine remodelling during menstruation. This is based on the ability of the metalloproteinases to cleave a broad range of matrix substrates such as collagen, proteoglycan and fibronectin. Metalloproteinases are also believed to be important in the processing, or secretion, of biologically important cell mediators, such as tumour necrosis factor-α (TNF-α); and the post translational proteolysis processing, or shedding, of biologically important membrane proteins, such as the low affinity IgE receptor CD23 (for a more complete list see N. M. Hooper *et al.*, (1997) Biochem J. 321:265-279).

Metalloproteinases have been associated with many disease conditions. Inhibition of the activity of one or more metalloproteinases may well be of benefit in these disease conditions, for example: various inflammatory and allergic diseases such as, inflammation of

the joint (especially rheumatoid arthritis, osteoarthritis and gout), inflammation of the gastro-intestinal tract (especially inflammatory bowel disease, ulcerative colitis and gastritis), inflammation of the skin (especially psoriasis, eczema, dermatitis); in tumour metastasis or invasion; in disease associated with uncontrolled degradation of the extracellular matrix such as osteoarthritis; in bone resorptive disease (such as osteoporosis and Paget's disease); in diseases associated with aberrant angiogenesis; the enhanced collagen remodelling associated with diabetes, periodontal disease (such as gingivitis), corneal ulceration, ulceration of the skin, post-operative conditions (such as colonic anastomosis) and dermal wound healing; demyelinating diseases of the central and peripheral nervous systems (such as multiple sclerosis); Alzheimer's disease; and extracellular matrix remodelling observed in cardiovascular diseases such as restenosis and atheroscelerosis.

A number of metalloproteinase inhibitors are known; different classes of compounds may have different degrees of potency and selectivity for inhibiting various metalloproteinases. We have discovered a class of compounds that are inhibitors of metalloproteinases and are of particular interest in inhibiting TACE. The compounds of this invention have beneficial potency and/or pharmacokinetic properties.

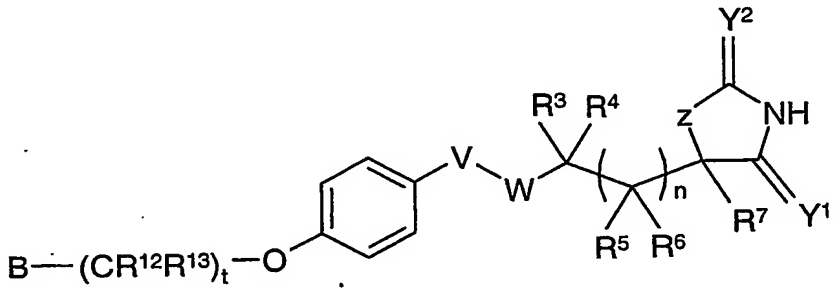
TACE (also known as ADAM17) which has been isolated and cloned [R.A. Black *et al.* (1997) Nature 385:729-733; M.L. Moss *et al.* (1997) Nature 385:733-736] is a member of the admalysin family of metalloproteins. TACE has been shown to be responsible for the cleavage of pro-TNF-α, a 26kDa membrane bound protein to release 17kDa biologically active soluble TNF-α. [Schlondorff *et al.* (2000) Biochem. J. 347: 131-138]. TACE mRNA is found in most tissues, however TNF-α is produced primarily by activated monocytes, macrophages and T lymphocytes. TNF-α has been implicated in a wide range of pro-inflammatory biological processes including induction of adhesion molecules and chemokines to promote cell trafficking, induction of matrix destroying enzymes, activation of fibroblasts to produce prostaglandins and activation of the immune system [Aggarwal *et al* (1996) Eur. Cytokine Netw. 7: 93-124]. Clinical use of the anti-TNF-α biologicals has shown TNF-α to play an important role in a range of inflammatory diseases including rheumatoid arthritis, Crohn's disease and psoriasis [Onrust *et al* (1998) Biodrugs 10: 397-422, Jarvis et al (1999) Drugs 57:945-964]. TACE activity has also been implicated in the shedding of other membrane bound proteins including TGFα, p75 & p55 TNF receptors, L-selectin and amyloid precursor protein [Black (2002) Int. J. Biochem. Cell Biol. 34: 1-5]. The biology of TACE

inhibition has recently been reviewed and shows TACE to have a central role in TNF-α production and selective TACE inhibitors to have equal, and possibly greater, efficacy in the collagen induced arthritis model of RA than strategies that directly neutralise TNF-α [Newton et al (2001) Ann. Rheum. Dis. 60: iii25-iii32].

A TACE inhibitor might therefore be expected to show efficacy in all disease where TNF-α has been implicated including, but not limited to, inflammatory diseases including rheumatoid arthritis and psoriasis, autoimmune diseases, allergic/atopic diseases, transplant rejection and graft versus host disease, cardiovascular disease, reperfusion injury, malignancy and other proliferative diseases.

We are able to provide compounds that have metalloproteinase inhibitory activity, and are in particular inhibitors of TACE (ADAM17).

According to the first aspect of the present invention there is provided a compound of formula (1), a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof:



formula (1)

wherein:

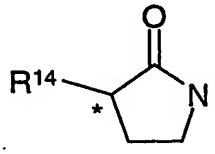
Y^1 and Y^2 are independently O or S;

z is NR^2, O or S;

n is 0 or 1;

W is NR^1, CR^1R^2 or a bond;

V is C(=O), $NR^{15}C(=O)$, $NR^{15}SO_2$, SO_2 or a group of formula (A):



formula (A)

where the group of formula (A) is bonded through nitrogen to W of formula (1) and through carbon * to phenyl of formula (1);

t is 0 or 1;

B is a group selected from aryl, heteroaryl and heterocyclyl where each group is optionally substituted by one or more groups independently selected from nitro, trifluoromethyl, trifluoromethoxy, halo, cyano, C_{1-4}alkyl (optionally substituted by R^9 or one or more halo), C_{2-4}alkenyl (optionally substituted by halo or R^9), C_{2-4}alkynyl (optionally substituted by halo or R^9), C_{3-6}cycloalkyl (optionally substituted by R^9 or one or more halo), C_{5-6}cycloalkenyl (optionally substituted by halo or R^9), aryl (optionally substituted by halo or C_{1-4}alkyl), heteroaryl (optionally substituted by halo or C_{1-4}alkyl), heterocyclyl (optionally substituted by C_{1-4}alkyl), $-SR^{11}$, $-SOR^{11}$, $-SO_2R^{11}$, $-SO_2NR^9R^{10}$, $-NR^9SO_2R^{11}$, $-NHCONR^9R^{10}$, $-OR^9$, $-NR^9R^{10}$, $-CONR^9R^{10}$ and $-NR^9COR^{10}$; or B is C_{2-4}alkenyl or C_{2-4}alkynyl, each being optionally substituted by a group selected from C_{1-4}alkyl, C_{3-6}cycloalkyl, aryl, heteroaryl, heterocyclyl whereby this group is optionally substituted by one or more halo, nitro, cyano, trifluoromethyl, trifluoromethoxy, $-CONHR^9$, $-CONR^9R^{10}$, $-SO_2R^{11}$, $-SO_2NR^9R^{10}$, $-NR^9SO_2R^{11}$, C_{1-4}alkyl and C_{1-4}alkoxy; with the provisos that:
when V is a group of formula (A), C(=O), $NR^{15}C(=O)$ or $NR^{15}SO_2$; or when V is SO_2 and n is 1 and W is NR^1, CR^1R^2 or a bond; or when V is SO_2 and n is 0 and W is CR^1R^2; then B is a group selected from aryl, heteroaryl and heterocyclyl where each group is optionally substituted by one or more groups independently selected from nitro, trifluoromethyl, trifluoromethoxy, halo, cyano, C_{1-4}alkyl (optionally substituted by R^9 or one or more halo), C_{2-4}alkenyl (optionally substituted by halo or R^9), C_{2-4}alkynyl (optionally substituted by halo or R^9), C_{3-6}cycloalkyl (optionally substituted by R^9 or one or more halo), C_{5-6}cycloalkenyl (optionally substituted by halo or R^9), aryl (optionally substituted by halo or C_{1-4}alkyl), heteroaryl (optionally substituted by halo or C_{1-4}alkyl), heterocyclyl (optionally substituted by

C_{1-4}alkyl), $-SR^{11}$, $-SOR^{11}$, $-SO_2R^{11}$, $-SO_2NR^9R^{10}$, $-NR^9SO_2R^{11}$, $-NHCONR^9R^{10}$, $-OR^9$, $-NR^9R^{10}$, $-CONR^9R^{10}$ and $-NR^9COR^{10}$; or B is C_{2-4}alkenyl or C_{2-4}alkynyl, each being optionally substituted by a group selected from C_{1-4}alkyl, C_{3-6}cycloalkyl, aryl, heteroaryl, heterocyclyl whereby this group is optionally substituted by one or more halo, nitro, cyano, trifluoromethyl, trifluoromethoxy, $-CONHR^9$, $-CONR^9R^{10}$, $-SO_2R^{11}$, $-SO_2NR^9R^{10}$, $-NR^9SO_2R^{11}$, C_{1-4}alkyl and C_{1-4}alkoxy; and

when V is SO_2 and n is 0 and W is NR^1 or a bond ; then B is a group selected from bicyclic aryl , bicyclic heteroaryl and bicyclic heterocyclyl, where each group is optionally substituted by one or more groups independently selected from nitro, trifluoromethyl, trifluoromethoxy, halo, cyano, C_{1-4}alkyl (optionally substituted by R^9 or one or more halo), C_{2-4}alkenyl (optionally substituted by halo or R^9), C_{2-4}alkynyl (optionally substituted by halo or R^9), C_{3-6}cycloalkyl (optionally substituted by R^9 or one or more halo), C_{5-6}cycloalkenyl (optionally substituted by halo or R^9), aryl (optionally substituted by halo or C_{1-4}alkyl), heteroaryl (optionally substituted by halo or C_{1-4}alkyl), heterocyclyl (optionally substituted by C_{1-4}alkyl), $-SR^{11}$, $-SOR^{11}$, $-SO_2R^{11}$, $-SO_2NR^9R^{10}$, $-NR^9SO_2R^{11}$, $-NHCONR^9R^{10}$, $-OR^9$, $-NR^9R^{10}$, $-CONR^9R^{10}$ and $-NR^9COR^{10}$; or B is C_{2-4}alkenyl or C_{2-4}alkynyl, each being optionally substituted by a group selected from C_{1-4}alkyl, C_{3-6}cycloalkyl, aryl, heteroaryl, heterocyclyl whereby this group is optionally substituted by one or more halo, nitro, cyano, trifluoromethyl, trifluoromethoxy, $-CONHR^9$, $-CONR^9R^{10}$, $-SO_2R^{11}$, $-SO_2NR^9R^{10}$, $-NR^9SO_2R^{11}$, C_{1-4}alkyl and C_{1-4}alkoxy;

R^1 and R^2 are independently hydrogen or a group selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl and C_{5-6}cycloalkenyl where the group may be optionally substituted by halo, cyano, nitro, hydroxy or C_{1-4}alkoxy;

R^3, R^4, R^5 and R^6 are independently hydrogen or a group selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{5-6}cycloalkenyl, aryl, heteroaryl and heterocyclyl where the group is optionally substituted by one or more substituents independently selected from halo, nitro, cyano, trifluoromethyl, trifluoromethyloxy, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{3-6}cycloalkyl (optionally substituted by one or more R^{17}), aryl (optionally substituted by one or more R^{17}), heteroaryl (optionally substituted by one or more R^{17}), heterocyclyl, $-OR^{18}$, $-SR^{19}$,

$-SOR^{19}$, $-SO_2R^{19}$, $-COR^{19}$, $-CO_2R^{18}$, $-CONR^{18}R^{20}$, $-NR^{16}COR^{18}$, $-SO_2NR^{18}R^{20}$ and $-NR^{16}SO_2R^{19}$;

or R^1 and R^3 together with the nitrogen or carbon and carbon to which they are respectively attached form a saturated 3-7-membered ring optionally containing 1 or 2 heteroatoms groups selected from NH, O, S, SO and SO_2 where the ring is optionally substituted on carbon or nitrogen by one or more C_{1-4}alkyl;

or R^3 and R^4 together form a saturated 3- to 7-membered ring optionally containing a heteroatom group selected from NH, O, S, SO and SO_2 where the ring is optionally substituted on carbon or nitrogen by one or more C_{1-4}alkyl;

or R^3 and R^5 together with the carbon atoms to which they are attached form a saturated 3- to 7-membered ring optionally containing a heteroatom group selected from NH, O, S, SO and SO_2 where the ring is optionally substituted on carbon or nitrogen by one or more C_{1-4}alkyl;

or R^5 and R^6 togetherform a saturated 3- to 7-membered ring optionally containing a heteroatom group selected from NH, O, S, SO and SO_2 where the ring is optionally substituted on carbon or nitrogen by one or more C_{1-4}alkyl;

R^7 is hydrogen or a group selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, heteroalkyl, C_{3-7}cycloalkyl, aryl, heteroaryl or heterocyclyl where the group is optionally substituted by halo, C_{1-4}alkyl, C_{1-4}alkoxy, C_{3-7}cycloalkyl, heterocyclyl, aryl, heteroaryl and heteroalkyl; and wherein the group from which R^7 may be selected is optionally substituted on the group and/or on its optional substituent by one or more substitutents independently selected from halo, cyano, C_{1-4}alkyl, nitro, haloC_{1-4}alkyl, heteroalkyl, aryl, heteroaryl, hydroxyC_{1-4}alkyl, C_{3-7}cycloalkyl, heterocyclyl, C_{1-4}alkoxyC_{1-4}alkyl, haloC_{1-4}alkoxyC_{1-4}alkyl, carboxyC_{1-4}alkyl, $-OR^{21}$, $-CO_2R^{21}$, $-SR^{25}$, $-SOR^{25}$, $-SO_2R^{25}$, $-NR^{21}COR^{22}$, $-CONR^{21}R^{22}$ and $-NHCONR^{21}R^{22}$;

or R^3 and R^7 together with the carbon atoms to which they are each attached and $(CR^5R^6)_n$ form a saturated 5- to 7-membered ring optionally containing a heteroatom group selected

from NH, O, S, SO and SO_2 where the ring is optionally substituted on carbon or nitrogen by one or more C_{1-4}alkyl;

R^8 is selected from hydrogen, C_{1-6}alkyl and haloC_{1-6}alkyl;

R^9 and R^{10} are independently hydrogen, C_{1-6}alkyl or C_{3-6}cycloalkyl;

or R^9 and R^{10} together with the nitrogen to which they are attached form a heterocyclic 4 to 7-membered ring;

R^{11} is C_{1-6}alkyl or C_{3-6}cycloalkyl;

R^{12} and R^{13} are independently selected from hydrogen, C_{1-6}alkyl and C_{3-6}cycloalkyl;

R^{14} is hydrogen, $-NR^{23}R^{24}$ or C_{1-4}alkyl (optionally substituted by halo, $-OR^{23}$ and $-NR^{23}R^{24}$);
R^{16}, R^{23} and R^{24} are independently hydrogen or C_{1-6}alkyl;

R^{17} is selected from halo, C_{1-6}alkyl, C_{3-6}cycloalkyl and C_{1-6}alkoxy;

R^{18} is hydrogen or a group selected from C_{1-6}alkyl, C_{3-6}cycloalkyl, C_{5-6}cycloalkenyl, saturated heterocyclyl, aryl, heteroaryl, arylC_{1-4}alkyl and heteroarylC_{1-4}alkyl where the group is optionally substituted by one or more halo;

R^{19} and R^{25} are independently a group selected from C_{1-6}alkyl, C_{3-6}cycloalkyl, C_{5-6}cycloalkenyl, saturated heterocyclyl, aryl, heteroaryl, arylC_{1-4}alkyl and heteroarylC_{1-4}alkyl where the group is optionally substituted by one or more halo;

R^{20} is hydrogen, C_{1-6}alkyl or C_{3-6}cycloalkyl;

or R^{18} and R^{20} together with the nitrogen to which they are attached form a heterocyclic 4- to 7- membered ring;

R^{21} and R^{22} are independently hydrogen, C_{1-4}alkyl, haloC_{1-4}alkyl, aryl, arylC_{1-4}alkyl and benzoyl.

According to a second aspect of the invention there is provided a compound of formula (1), a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof wherein:

Y^1 and Y^2 are independently O or S;

z is NR^8, O or S;

n is 0;

W is NR^1 or a bond;

V is SO_2;

t is 0 or 1;

B is a group selected from aryl, heteroaryl and heterocyclyl where each group is optionally substituted by one or more groups independently selected from nitro, trifluoromethyl, trifluoromethoxy, halo, cyano, C_{1-4}alkyl (optionally substituted by R^9 or one or more halo), C_{2-4}alkenyl (optionally substituted by halo or R^9), C_{2-4}alkynyl (optionally substituted by halo or R^9), C_{3-6}cycloalkyl (optionally substituted by R^9 or one or more halo), C_{5-6}cycloalkenyl (optionally substituted by halo or R^9), aryl (optionally substituted by halo or C_{1-4}alkyl), heteroaryl (optionally substituted by halo or C_{1-4}alkyl), heterocyclyl (optionally substituted by C_{1-4}alkyl), $-SR^9$, $-SOR^{11}$, $-SO_2R^9$, $-SO_2NR^9R^{10}$, $-NR^9SO_2R^{11}$, $-NHCONR^9R^{10}$, $-OR^9$, $-CONR^9R^{10}$ and $-NR^9COR^{10}$; or B is C_{2-4}alkenyl or C_{2-4}alkynyl, each being optionally substituted by a group selected from C_{1-4}alkyl, C_{3-6}cycloalkyl, aryl, heteroaryl, heterocyclyl whereby this group is optionally substituted by one or more halo, nitro, cyano, trifluoromethyl, trifluoromethoxy, $-CONHR^9$, $-CONR^9R^{10}$, $-SO_2R^{11}$, $-SO_2NR^9R^{10}$, $-NR^9SO_2R^{11}$, C_{1-4}alkyl and C_{1-4}alkoxy;

provided that when t is 0 and B is monocyclic aryl, monocyclic heteroaryl or monocyclic heterocyclyl then the monocyclic group that is B is substituted on the carbon or nitrogen adjacent to the atom to which the oxygen is attached, by a group described above;

R^1 is hydrogen or a group selected from C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{3-5}cycloalkyl and cyclopentenyl where the group may be optionally substituted by halo, cyano, nitro, hydroxy or C_{1-4}alkoxy;

R^3 and R^4 are independently hydrogen or a group selected from C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{3-4}cycloalkyl, cyclopentenyl, aryl, heteroaryl and heterocyclyl where the group is optionally substituted by one or more substituents independently selected from halo, nitro, cyano, trifluoromethyl, trifluoromethyloxy, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{3-6}cycloalkyl (optionally substituted by one or more R^{17}), aryl (optionally substituted by one or more R^{17}), heteroaryl (optionally substituted by one or more R^{17}), heterocyclyl, $-OR^{18}$, $-SR^{19}$, $-SOR^{19}$, $-SO_2R^{19}$, $-CONR^{18}R^{20}$ and $-NR^{16}COR^{18}$;

or R^1 and R^3 together with the nitrogen or carbon and carbon to which they are respectively attached form a saturated 3-7-membered ring optionally containing 1 or 2 heteroatoms groups selected form NH, O, S, SO and SO_2 where the ring is optionally substituted on carbon or nitrogen by one or more C_{1-4}alkyl;

or R^3 and R^4 together form a saturated 3- to 7-membered ring optionally containing a heteroatom group selected from NH, O, S, SO and SO_2 where the ring is optionally substituted on carbon or nitrogen by one or more C_{1-4}alkyl

R^7 is hydrogen or a group selected from C_{1-4}alkyl, heteroalkyl, C_{3-5}cycloalkyl, aryl, heteroaryl or heterocyclyl where the group is optionally substituted by halo, C_{1-4}alkyl, C_{1-4}alkoxy, C_{3-5}cycloalkyl, heterocyclyl, aryl, heteroaryl and heteroalkyl; and wherein the group from which R^7 may be selected is optionally substituted on the group and/or on its optional substituent by one or more substitutents independently selected from halo, cyano, C_{1-4}alkyl, nitro, haloC_{1-4}alkyl, heteroalkyl, aryl, heteroaryl, hydroxyC_{1-4}alkyl, C_{3-5}cycloalkyl, heterocyclyl, C_{1-}

$_4$alkoxyC_{1-4}alkyl, haloC_{1-4}alkoxyC_{1-4}alkyl, carboxyC_{1-4}alkyl, $-OR^{21}$, $-CO_2R^{21}$, $-SR^{25}$, $-SOR^{25}$, $-SO_2R^{25}$, $-CONR^{21}R^{22}$ and $-NHCONR^{21}R^{22}$;

or R^3 and R^7 together with the carbon atoms to which they are attached form a saturated 5- to 7-membered ring optionally containing a heteroatom group selected from NH, O, S and SO_2 where the ring is optionally substituted on carbon or nitrogen by one or more C1-4alkyl;

R^8 is selected from hydrogen, C_{1-4}alkyl and haloC_{1-4}alkyl;

R^9 and R^{10} are independently hydrogen, C_{1-4}alkyl or C_{3-5}cycloalkyl;

or R^9 and R^{10} together with the nitrogen to which they are attached form a heterocyclic 4 to 7-membered ring.

R^{11} is C_{1-4}alkyl or C_{3-5}cycloalkyl;

R^{12} and R^{13} are independently selected from hydrogen, C_{1-4}alkyl and C_{3-4}cycloalkyl;

R^{16} is hydrogen or C_{1-4}alkyl;

R^{17} is selected from halo, C_{1-4}alkyl, C_{3-5}cycloalkyl and C_{1-4}alkoxy;

R^{18} is hydrogen or a group selected from C_{1-4}alkyl, C_{3-5}cycloalkyl, C_{5-6}cycloalkenyl, saturated heterocyclyl, aryl, heteroaryl, arylC_{1-4}alkyl and heteroarylC_{1-4}alkyl where the group is optionally substituted by one or more halo;

R^{19} and R^{25} are independently a group selected from C_{1-4}alkyl, C_{3-5}cycloalkyl, C_{5-6}cycloalkenyl, saturated heterocyclyl, aryl, heteroaryl, arylC_{1-4}alkyl and heteroarylC_{1-4}alkyl where the group is optionally substituted by one or more halo;

R^{20} is hydrogen, C_{1-4}alkyl or C_{3-5}cycloalkyl;

or R^{18} and R^{20} together with the nitrogen to which they are attached form a heterocyclic 4- to 6- membered ring;

R^{21} and R^{22} are independently hydrogen, C_{1-4}alkyl, haloC_{1-4}alkyl, aryl, arylC_{1-4}alkyl and benzoyl.

It is to be understood that, insofar as certain of the compounds of formula (1) defined above may exist in optically active or racemic forms by virtue of one or more asymmetric carbon or sulphur atoms, the invention includes in its definition any such optically active or racemic form which possesses metalloproteinases inhibition activity and in particular TACE inhibition activity. The synthesis of optically active forms may be carried out by standard techniques of organic chemistry well known in the art, for example by synthesis from optically active starting materials or by resolution of a racemic form. Similarly, the above-mentioned activity may be evaluated using the standard laboratory techniques referred to hereinafter.

Compounds of formula (1) are therefore provided as enantiomers, diastereomers, geometric isomers and atropisomers.

Within the present invention it is to be understood that a compound of the formula (1) or a salt thereof may exhibit the phenomenon of tautomerism and that the formulae drawings within this specification can represent only one of the possible tautomeric forms. It is to be understood that the invention encompasses any tautomeric form which has metalloproteinases inhibition activity and in particular TACE inhibition activity and is not to be limited merely to any one tautomeric form utilised within the formulae drawings. The formulae drawings within this specification can represent only one of the possible tautomeric forms and it is to be understood that the specification encompasses all possible tautomeric forms of the compounds drawn not just those forms which it has been possible to show graphically herein.

It is also to be understood that certain compounds of the formula (1) and salts thereof can exist in solvated as well as unsolvated forms such as, for example, hydrated forms. It is to be understood that the invention encompasses all such solvated forms which have metalloproteinases inhibition activity and in particular TACE inhibition activity.

It is also to be understood that certain compounds of the formula (1) may exhibit polymorphism, and that the invention encompasses all such forms which possess metalloproteinases inhibition activity and in particular TACE inhibition activity.

The present invention relates to the compounds of formula (1) as hereinbefore defined as well as to the salts thereof. Salts for use in pharmaceutical compositions will be pharmaceutically acceptable salts, but other salts may be useful in the production of the compounds of formula (1) and their pharmaceutically acceptable salts. Pharmaceutically acceptable salts of the invention may, for example, include acid addition salts of the compounds of formula (1) as hereinbefore defined which are sufficiently basic to form such salts. Such acid addition salts include but are not limited to hydrochloride, hydrobromide, citrate and maleate salts and salts formed with phosphoric and sulphuric acid. In addition where the compounds of formula (1) are sufficiently acidic, salts are base salts and examples include but are not limited to, an alkali metal salt for example sodium or potassium, an alkaline earth metal salt for example calcium or magnesium, or organic amine salt for example triethylamine or tris-(2-hydroxyethyl)amine

The compounds of formula (1) may also be provided as *in vivo* hydrolysable esters. An *in vivo* hydrolysable ester of a compound of formula (1) containing carboxy or hydroxy group is, for example a pharmaceutically acceptable ester which is cleaved in the human or animal body to produce the parent acid or alcohol. Such esters can be identified by administering, for example, intravenously to a test animal, the compound under test and subsequently examining the test animal's body fluid.

Suitable pharmaceutically acceptable esters for carboxy include C_{1-6}alkoxymethyl esters for example methoxymethyl, C_{1-6}alkanoyloxymethyl esters for example pivaloyloxymethyl, phthalidyl esters, C_{3-8}cycloalkoxycarbonyloxyC_{1-6}alkyl esters for example 1-cyclohexylcarbonyloxyethyl; 1,3-dioxolen-2-onylmethyl esters for example 5-methyl-1,3-dioxolen-2-onylmethyl; and C_{1-6}alkoxycarbonyloxyethyl esters for example 1-methoxycarbonyloxyethyl and may be formed at any carboxy group in the compounds of this invention.

Suitable pharmaceutically-acceptable esters for hydroxy include inorganic esters such as phosphate esters (including phosphoramidic cyclic esters) and α-acyloxyalkyl ethers and related compounds which as a result of the *in-vivo* hydrolysis of the ester breakdown to give the parent hydroxy group/s. Examples of α-acyloxyalkyl ethers include acetoxymethoxy and 2,2-dimethylpropionyloxymethoxy. A selection of *in-vivo* hydrolysable ester forming groups for hydroxy include C_{1-10}alkanoyl, for example formyl, acetyl; benzoyl; phenylacetyl; substituted benzoyl and phenylacetyl, C_{1-10}alkoxycarbonyl (to give alkyl carbonate esters), for

example ethoxycarbonyl; di-(C_{1-4})alkylcarbamoyl and *N*-(di-(C_{1-4})alkylaminoethyl)-*N*-(C_{1-4})alkylcarbamoyl (to give carbamates); di-(C_{1-4})alkylaminoacetyl and carboxyacetyl. Examples of ring substituents on phenylacetyl and benzoyl include aminomethyl, (C_{1-4})alkylaminomethyl and di-((C_{1-4})alkyl)aminomethyl, and morpholino or piperazino linked from a ring nitrogen atom via a methylene linking group to the 3- or 4- position of the benzoyl ring. Other interesting in-vivo hydrolysable esters include, for example, $R^A C(O)O(C_{1-6})$alkyl-CO-, wherein R^A is for example, benzyloxy-(C_{1-4})alkyl, or phenyl). Suitable substituents on a phenyl group in such esters include, for example, 4-(C_{1-4})piperazino-(C_{1-4})alkyl, piperazino-(C_{1-4})alkyl and morpholino-(C_{1-4})alkyl.

In this specification the generic term "alkyl" includes both straight-chain and branched-chain alkyl groups. However references to individual alkyl groups such as "propyl" are specific for the straight chain version only and references to individual branched-chain alkyl groups such as *t*-butyl are specific for the branched chain version only. For example, "C_{1-4}alkyl" includes methyl, ethyl, propyl, isopropyl, butyl and *t*-butyl and examples of "C_{1-6}alkyl" include the examples of "C_{1-4}alkyl"and additionally pentyl, 2,3-dimethylpropyl, 3-methylbutyl and hexyl. An analogous convention applies to other generic terms, for example "C_{2-4}alkenyl" includes vinyl, allyl and 1-propenyl and examples of "C_{2-6}alkenyl" include the examples of "C_{2-4}alkenyl" and additionally 1-butenyl, 2-butenyl, 3-butenyl, 2-methylbut-2-enyl, 3-methylbut-1-enyl, 1-pentenyl, 3-pentenyl and 4-hexenyl. Examples of "C_{2-4}alkynyl" includes ethynyl, 1-propynyl, 2-propynyl, 3-butynyl and examples of "C_{2-6}alkynyl"include the examples of "C_{2-4}alkynyl" and additionally 2-pentynyl, hexynyl and 1-methylpent-2-ynyl. Where examples are given for generic terms, it should be noted that these examples are not limiting.

"Cycloalkyl" is a monocyclic, saturated alkyl ring. The term "C_{3-4}cycloalkyl" includes cyclopropyl and cyclobutyl. The term "C_{3-5}cycloalkyl" includes "C_{3-4}cycloalkyl and cyclopentyl. The term "C_{3-6}cycloalkyl" includes "C_{3-5}cycloalkyl", and cyclohexyl. The term "C_{3-7}cycloalkyl" includes "C_{3-6}cycloalkyl" and additionally cycloheptyl. The term "C_{3-10}cycloalkyl" includes "C_{3-7}cycloalkyl" and additionally cyclooctyl, cyclononyl and cyclodecyl.

"Cycloalkenyl" is a monocyclic ring containing 1, 2, 3 or 4 double bonds. Examples of "C_{5-6}cycloalkenyl" are cyclopentenyl, cyclohexenyl and cyclohexadiene and examples of "C_{5-10}cycloalkenyl" include the examples of "C_{5-6}cycloalkenyl" and cyclooctatriene.

Unless otherwise specified "aryl" is monocyclic or bicyclic. Examples of "aryl" therefore include phenyl (an example of monocyclic aryl) and naphthyl (an example of bicyclic aryl).

Examples of "arylC_{1-4}alkyl" are benzyl, phenethyl, naphthylmethyl and naphthylethyl.

Unless otherwise specified "heteroaryl" is a monocyclic or bicyclic aryl ring containing 5 to 10 ring atoms of which 1, 2, 3 or 4 ring atoms are chosen from nitrogen, sulphur or oxygen where a ring nitrogen or sulphur may be oxidised. Examples of heteroaryl are pyridyl, imidazolyl, quinolinyl, cinnolyl, pyrimidinyl, thienyl, pyrrolyl, pyrazolyl, thiazolyl, oxazolyl, isoxazolyl and pyrazinyl. Preferably heteroaryl is pyridyl, imidazolyl, quinolinyl, pyrimidinyl, thienyl, pyrazolyl, thiazolyl, oxazolyl and isoxazolyl. More preferably heteroaryl is pyridyl, imidazolyl and pyrimidinyl. Examples of "monocyclic heteroaryl" are pyridyl, imidazolyl, pyrimidinyl, thienyl, pyrrolyl, pyrazolyl, thiazolyl, oxazolyl, isoxazolyl and pyrazinyl. Examples of "bicyclic heteroaryl" are quinolinyl and cinnolinyl.

Examples of "heteroarylC_{1-4}alkyl" are pyridylmethyl, pyridylethyl, pyrimidinylethyl, pyrimidinylpropyl, pyrimidinylbutyl, imidazolylpropyl, imidazolylbutyl, quinolinylpropyl, 1,3,4-triazolylpropyl and oxazolylmethyl.

"Heterocyclyl" is a saturated, partially saturated or unsaturated, monocyclic or bicyclic ring (unless otherwise stated) containing 4 to 12 atoms of which 1, 2, 3 or 4 ring atoms are chosen from nitrogen, sulphur or oxygen, which may, unless otherwise specified, be carbon or nitrogen linked, wherein a -CH_2- group can optionally be replaced by a -C(O)-; and where unless stated to the contrary a ring nitrogen or sulphur atom is optionally oxidised to form the N-oxide or S-oxide(s); a ring –NH is optionally substituted by acetyl, formyl, methyl or mesyl; and a ring is optionally substituted by one or more halo. Examples and suitable values of the term "heterocyclyl" are piperidinyl, *N*-acetylpiperidinyl, *N*-methylpiperidinyl, *N*-formylpiperazinyl, *N*-mesylpiperazinyl, homopiperazinyl, piperazinyl, azetidinyl, oxetanyl, morpholinyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, indolinyl, pyranyl, dihydro-*2H*-pyranyl, tetrahydrofuranyl, 2,5-dioximidazolidinyl, 2,2-dimethyl-1,3-dioxolanyl and 3,4-dimethylenedioxybenzyl. Preferred values are 3,4-dihydro-*2H*-pyran-5-yl, tetrahydrofuran-2-

yl, 2,5-dioximidazolidinyl, 2,2-dimethyl-1,3-dioxolan-2-yl and 3,4-dimethylenedioxybenzyl. Examples of monocyclic heterocyclyl are piperidinyl, *N*-acetylpiperidinyl, *N*-methylpiperidinyl, *N*-formylpiperazinyl, *N*-mesylpiperazinyl, homopiperazinyl, piperazinyl, azetidinyl, oxetanyl, morpholinyl, pyranyl, tetrahydrofuranyl, 2,5-dioximidazolidinyl and 2,2-dimethyl-1,3-dioxolanyl. Examples of bicyclic heterocyclyl are tetrahydroisoquinolinyl, tetrahydroquinolinyl, indolinyl and 3,4-dimethylenedioxybenzyl. Examples of saturated heterocyclyl are piperidinyl, pyrrolidinyl and morpholinyl.

The term "halo" refers to fluoro, chloro, bromo and iodo.

Examples of "C_{1-4}alkoxy" include methoxy, ethoxy, propoxy and isopropoxy. Examples of "C_{1-6}alkoxy" include the examples of "C_{1-4}alkoxy" and additionally pentyloxy, 1-ethylpropoxy and hexyloxy.

"Heteroalkyl" is alkyl containing at least one carbon atom and having at least one carbon atom replaced by a hetero group independently selected from N, O, S, SO, SO_2, (a hetero group being a hetero atom or group of atoms).

Examples of "haloC_{1-4}alkyl" include fluoromethyl, 1-chloroethyl, 2-chloroethyl, 2-bromopropyl, 1-fluoroprop-2-yl and 4-chlorobutyl. Examples of "haloC_{1-6}alkyl" include the examples of "haloC_{1-4}alkyl" and 1-chloropentyl, 3-chloropentyl and 2-fluorohexyl.

Examples of "hydroxyC_{1-4}alkyl" include hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl, 2-hydroxypropyl, 1-hydroxyprop-2-yl and 4-hydroxybutyl.

Example of "C_{1-4}alkoxyC_{1-4}alkyl" include methoxymethyl, ethoxymethyl, methoxyethyl, methoxypropyl and propoxybutyl.

Examples of "haloC_{1-4}alkoxyC_{1-4}alkyl" include 1-(chloromethoxy)ethyl, 2-fluoroethoxymethyl, 2-(4-bromobutoxy)ethyl and 2-(2-iodoethoxy)ethyl.

Examples of "carboxyC_{1-4}alkyl" include carboxymethyl, 2-carboxyethyl and 2-carboxypropyl.

Heterocyclic rings are rings containing 1, 2 or 3 ring atoms selected from nitrogen, oxygen and sulphur. "Heterocyclic 5 to 7-membered" rings are pyrrolidinyl, piperidinyl, piperazinyl, homopiperidinyl, homopiperazinyl, thiomorpholinyl , thiopyranyl and morpholinyl. "Heterocyclic 4 to 7-membered" rings include the examples of "heterocyclic 5 to 7-membered" and additionally azetidinyl.

Where optional substituents are chosen from "one of more" groups or substituents it is to be understood that this definition includes all substituents being chosen from one of the

specified groups or the substituents being chosen from two or more of the specified groups. Preferably "one or more" means "1, 2 or 3" and this is particularly the case when the group or substituent is halo. "One or more" may also means "1 or 2".

Compounds of the present invention have been named with the aid of computer software (ACD/Name version 5.09).

Preferred values of Y^1, Y^2, z, n, W, V, t, B, R^3, R^4, R^5, R^6, R^7, R^{12} and R^{13} are as follows. Such values may be used where appropriate with any of the definitions, claims or embodiments defined hereinbefore or hereinafter.

In one aspect of the invention Y^1 and Y^2 are both O.

In another aspect Y^1 and Y^2 are both S.

In one aspect of the invention z is NR^8.

In one aspect of the invention n is 1.

In another aspect n is 0.

In one aspect of the invention W is NR^1.

In another aspect W is CR^1R^2.

In a further aspect W is a bond.

In one aspect of the invention V is C(=O), $NR^{15}C(=O)$, $NR^{15}SO_2$ or a group of formula (A).

In one aspect of the invention V is a group of formula (A).

In another aspect of the invention V is SO_2.

In another aspect of the invention V is C(=O).

In another aspect of the invention V is $NR^{15}C(=O)$.

In another aspect of the invention V is $NR^{15}SO_2$.

In one aspect of the invention t is 0.

In another aspect of the invention t is 1.

In one aspect of the invention, when V is a group of formula (A), C(=O), $NR^{15}C(=O)$ or $NR^{15}SO_2$; or when V is SO_2 and n is 1 and W is NR^1, CR^1R^2 or a bond; or when V is SO_2 and n is 0 and W is CR^1R^2; then B is a group selected from aryl, heteroaryl and heterocyclyl where each group is optionally substituted by one or more groups independently selected from nitro, trifluoromethyl, trifluoromethoxy, halo, C_{1-4}alkyl (optionally substituted by one or more halo), C_{2-4}alkynyl, heteroaryl, $-OR^9$, cyano, $-NR^9R^{10}$, $-CONR^9R^{10}$ and $-NR^9COR^{10}$; or B is C_{2-4}alkenyl or C_{2-4}alkynyl optionally substituted by C_{1-4}alkyl, C_{3-6}cycloalkyl or heterocyclyl.

In another aspect, when V is a group of formula (A), C(=O), $NR^{15}C(=O)$ or $NR^{15}SO_2$; or when V is SO_2 and n is 1 and W is NR^1, CR^1R^2 or a bond; or when V is SO_2 and n is 0 and W is CR^1R^2; then B is phenyl, naphthyl, pyridyl, quinolinyl, isoquinolinyl, thieno[2,3-*b*]pyridyl, thieno[3,2-*b*]pyridyl, 1,8-naphthyridinyl, 3,4-methylenedioxybenzyl, 1,6-naphthyridinyl, thieno[2,3-*d*]pyrimidinyl or thieno[3,2-*d*]pyrimidinyl where each is optionally substituted by one or more groups independently selected from nitro, trifluoromethyl, trifluoromethoxy, halo, C_{1-4}alkyl (optionally substituted by one or more fluoro), C_{2-4}alkynyl, heteroaryl, $-OR^9$, cyano, $-NR^9R^{10}$, $-CONR^9R^{10}$ and $-NR^9COR^{10}$; or B is vinyl or ethynyl optionally substituted by C_{1-4}alkyl.

In another aspect when V is a group of formula (A), C(=O), $NR^{15}C(=O)$ or $NR^{15}SO_2$; or when V is SO_2 and n is 1 and W is NR^1, CR^1R^2 or a bond; or when V is SO_2 and n is 0 and W is CR^1R^2; then B is phenyl, naphthyl, pyridyl, quinolinyl, isoquinolinyl, thieno[2,3-*b*]pyridyl, thieno[3,2-*b*]pyridyl, 1,8-naphthyridinyl, 3,4-methylenedioxybenzyl, 1,6-naphthyridinyl, thieno[2,3-*d*]pyrimidinyl or thieno[3,2-*d*]pyrimidinyl where each is optionally substituted by one or more groups independently selected from trifluoromethyl, trifluoromethoxy, fluoro, chloro, bromo, methyl, isopropyl, ethynyl, cyano, acetamido, propyloxy, prop-2-yloxy, methoxy, nitro, pyrrolidinylcarbonyl, *N*-propylcarbamoyl, pyrrolidinyl, piperidinyl, isoxazolyl, pyrazolyl, imidazolyl, oxazolyl, thiazolyl, pyrimidinyl and pyridyl; or B is vinyl or ethynyl optionally substituted by methyl or ethyl.

In a further aspect when V is a group of formula (A), C(=O), $NR^{15}C(=O)$ or $NR^{15}SO_2$; or when V is SO_2 and n is 1 and W is NR^1, CR^1R^2 or a bond; or when V is SO_2 and n is 0 and W is CR^1R^2; then B is quinolin-4-yl, naphthyl, 2-methylquinolin-4-yl, 3-methylnaphthyl, 7-

methylquinolin-5-yl, 6-methylquinolin-8-yl, 7-methylisoquinolin-5-yl, 6-methylthieno[2,3-*b*]pyridyl, 5-methylthieno[3,2-*b*]pyridyl, 2-methyl-1,8-naphthyridinyl, 2-trifluoromethylquinolin-4-yl, 2-ethynylquinolin-4-yl, 7-chloroquinolin-5-yl, 7-fluoro-2-methylquinolin-4-yl, 2-methyl-*N*-oxoquinolin-4-yl, 3-methylisoquinolin-1-yl, 5-fluoro-2-methylquinolin-4-yl, 2,6-dimethylpyrid-4-yl, 2,5-dimethylpyridin-4-yl, 2,5-dimethylphenyl, 3-methoxyphenyl, 2,5-difluorophenyl, 3,5-difluorophenyl, pyrid-2-yl, pyrid-3-yl, pyrid-4-yl, 2,6-difluoro-3-methylphenyl, 2-chloro-6-fluorophenyl, 3-fluoro-6-methylphenyl, phenyl, 2-methylphenyl, 3-chlorophenyl, 2-bromophenyl, 2-fluorophenyl, 2,6-difluorophenyl, 3-fluorophenyl, 4-trifluoromethylphenyl, 2-chlorophenyl, 3,4-dichlorophenyl, 4-chlorophenyl, 4-bromophenyl, 2-cyanophenyl, 4-fluorophenyl, 2-fluoro-3-methylphenyl, 4-methylphenyl, 2,4-dichlorophenyl, 2,6-dichlorophenyl, 2,4,6-trimethylphenyl, 3-methylphenyl, 3,4-dimethylphenyl, 4-methoxyphenyl, 3,5-dimethylphenyl, 4-prop-2-ylphenyl, 3-chloro-4-methylphenyl, 3,4-methylenedioxybenzyl, 5-fluoro-2-methylpyridinyl, 2,4-dimethylphenyl, 1-methylquinolinyl, 2-chloro-4-fluorophenyl, 2-chloro-4-trifluoromethylphenyl, 2-bromo-4,6-difluorophenyl, 2-bromo-4-fluorophenyl, 2,4-dichlorophenyl, 2-cyanophenyl, 2-bromophenyl, 2-chlorophenyl, 2-acetamidophenyl, 2-(prop-2-yloxy)phenyl, 2-trifluoromethylphenyl, 2-bromo-4-chlorophenyl, 2-methoxy-4-methylphenyl, 4-chloro-2-nitrophenyl, 4-methyl-2-nitrophenyl, 2,4-difluorophenyl, 2-nitrophenyl, 4-bromo-2-fluorophenyl, 2-methoxy-4-nitrophenyl, 2-(pyrrolidin-1-ylcarbonyl)phenyl, 2-chloro-4-nitrophenyl, 2-(*N*-prop-2-yl)carbamoylphenyl, 2-(pyrrolidin-1-yl)phenyl, 2-(piperidin-1-yl)phenyl, 4-bromo-2-methoxyphenyl, 2-fluoro-4-nitrophenyl, 2-chloro-4-bromophenyl, 2-chloro-4-methylphenyl, 2-chloro-4-methoxyphenyl, 4-fluoro-2-methoxyphenyl, 2-fluoro-4-chlorophenyl, 4-fluoro-2-methylphenyl, 2-(isoxazol-5-yl)phenyl, 3-chloropyrid-2-yl, 7-chloroquinolin-4-yl, 3-cyanopyrid-2-yl, 8-chloroquinolin-4-yl, 3-trifluormethylpyrid-2-yl, 3-chloro-5-trifluoromethylpyrid-2-yl, 3,5-dichloropyrid-2-yl, 6-chloroquinolin-4-yl, 5-methylthieno[2,3-*d*]pyrimidin-4-yl, 7-methylthieno[3,2-*d*]pyrimidin-4-yl, 8-fluoroquinolin-4-yl, 2-pyrazol-5-ylphenyl, 4-chloro-2-(isoxazol-5-yl)phenyl, 2-(isoxazol-5-yl)-4-trifluoromethylphenyl, 2-imidazol-5-ylphenyl, 2-(oxazol-5-yl)phenyl, 2-(thiazol-5-yl)phenyl, 2-(pyrimidin-2-yl)phenyl, 2-(pyrid-2-yl)phenyl, 6-fluoroquinolin-4-yl, 2-methylquinolin-4-yl, 6-chloro-2-methylquinolin-4-yl, 1,6-naphthyridin-4-yl, thieno[3,2-*b*]pyrid-7-yl, 5-fluoro-2-(isoxazol-5-yl)phenyl, 4-fluoro-2-(isoxazol-5-yl)phenyl, 4-chloro-2-trifluoromethylphenyl, 2-chloro-5-fluorophenyl, vinyl, ethynyl, prop-1-enyl, prop-1-ynyl or but-1-ynyl.

In one aspect of the invention, when V is SO_2 and n is 0 and W is NR^1 or a bond; B is a group selected from bicyclic aryl, bicyclic heteroaryl and bicyclic heterocyclyl, where each group is optionally substituted by one or more groups independently selected from nitro, trifluoromethyl, trifluoromethoxy, halo, C_{1-4}alkyl (optionally substituted by one or more halo), C_{2-4}alkynyl, heteroaryl, $-OR^9$, cyano, $-NR^9R^{10}$, $-CONR^9R^{10}$ and $-NR^9COR^{10}$; or B is C_{2-4}alkenyl or C_{2-4}alkynyl optionally substituted by C_{1-4}alkyl, C_{3-6}cycloalkyl or heterocyclyl.

In another aspect when V is SO_2 and n is 0 and W is NR^1 or a bond; B is naphthyl, quinolinyl, isoquinolinyl, thieno[2,3-*b*]pyridyl, thieno[3,2-*b*]pyridyl, 1,8-naphthyridinyl, 3,4-methylenedioxybenzyl, 1,6-naphthyridinyl, thieno[2,3-*d*]pyrimidinyl or thieno[3,2-*d*]pyrimidinyl where each is optionally substituted by one or more groups independently selected from nitro, trifluoromethyl, trifluoromethoxy, halo, C_{1-4}alkyl (optionally substituted by one or more fluoro), C_{2-4}alkynyl, heteroaryl, $-OR^9$, cyano, $-NR^9R^{10}$, $-CONR^9R^{10}$ and $-NR^9COR^{10}$; or B is vinyl or ethynyl optionally substituted by C_{1-4}alkyl.

In another aspect when V is SO_2 and n is 0 and W is NR^1 or a bond; B is naphthyl, quinolinyl, isoquinolinyl, thieno[2,3-*b*]pyridyl, thieno[3,2-*b*]pyridyl, 1,8-naphthyridinyl, 3,4-methylenedioxybenzyl, 1,6-naphthyridinyl, thieno[2,3-*d*]pyrimidinyl or thieno[3,2-*d*]pyrimidinyl where each is optionally substituted by one or more groups independently selected from trifluoromethyl, trifluoromethoxy, fluoro, chloro, bromo, methyl, isopropyl, ethynyl, cyano, acetamido, propyloxy, prop-2-yloxy, methoxy, nitro, pyrrolidinylcarbonyl and *N*-propylcarbamoyl; or B is vinyl or ethynyl optionally substituted by methyl or ethyl.

In another aspect when V is SO_2 and n is 0 and W is NR^1 or a bond; B is quinolin-4-yl, naphthyl, 2-methylquinolin-4-yl, 3-methylnaphthyl, 7-methylquinolin-5-yl, 6-methylquinolin-8-yl, 7-methylisoquinolin-5-yl, 6-methylthieno[2,3-b]pyridyl, 5-methylthieno[3,2-b]pyridyl, 2-methyl-1,8-naphthyridinyl, 2-trifluoromethylquinolin-4-yl, 2-ethynylquinolin-4-yl, 7-chloroquinolin-5-yl, 7-fluoro-2-methylquinolin-4-yl, 2-methyl-*N*-oxoquinolin-4-yl, 3-methylisoquinolin-1-yl, 5-fluoro-2-methylquinolin-4-yl, 3,4-methylenedioxybenzyl, 1-methylquinolinyl, 7-chloroquinolin-4-yl, 8-chloroquinolin-4-yl, 6-chloroquinolin-4-yl, 5-methylthieno[2,3-*d*]pyrimidin-4-yl, 7-methylthieno[3,2-*d*]pyrimidin-4-yl, 8-fluoroquinolin-4-

yl, 6-fluoroquinolin-4-yl, 2-methylquinolin-4-yl, 6-chloro-2-methylquinolin-4-yl, 1,6-naphthyridin-4-yl, thieno[3,2-*b*]pyrid-7-yl, vinyl, ethynyl, prop-1-enyl, prop-1-ynyl or but-1-ynyl.

In one aspect of the invention B is a group selected from aryl and heteroaryl where each group is optionally substituted by one or more groups independently selected from halo, C_{1-4}alkyl (optionally substituted by one or more halo), C_{2-4}alkenyl (optionally substituted by halo) and C_{2-4}alkynyl (optionally substituted by halo); or B is C_{2-4}alkenyl or C_{2-4}alkynyl, each being optionally substituted by a group selected from C_{1-4}alkyl, C_{3-6}cycloalkyl, aryl, heteroaryl, heterocyclyl whereby this group is optionally substituted by one or more halo, nitro, cyano, trifluoromethyl, trifluoromethoxy, $-CONHR^9$, $-CONR^9R^{10}$, $-SO_2R^{11}$, $-SO_2NR^9R^{10}$, $-NR^9SO_2R^{11}$, C_{1-4}alkyl and C_{1-4}alkoxy;

provided that when t is 0 and B is monocyclic aryl or monocyclic heteroaryl then the monocyclic group that is B is substituted on the carbon or nitrogen adjacent to the atom to which the oxygen is attached, by a substituent group described above.

In another aspect of the invention B is a group selected from quinolinyl, pyridyl and phenyl where each group is optionally substituted by one or more methyl, trifluoromethyl, trifluoromethoxy, halo or isoxazolyl.

In a further aspect of the invention B is 2-methylquinolin-4-yl, 2,5-dimethylphenyl or 2,5-dimethylpyrid-4-yl.

In one aspect of the invention R^1 is hydrogen or methyl.

In one aspect of the invention R^2 is hydrogen or methyl.

In one aspect of the invention R^3 is hydrogen, methyl, propyl or phenyl.

In one aspect of the invention R^1 and R^3 together with the nitrogen or carbon and carbon to which they are respectively attached form a 2,2-dimethylthiomorpholine, piperidine, pyrrolidine, piperazine, morpholine, cyclopentane or cyclohexane ring.

In one aspect of the invention R^4 is hydrogen or methyl.

In one aspect of the invention R^3 and R^4 together form a pyrrolidine ring or a tetrahydro-2H-pyran ring.

In one aspect of the invention R^5 is hydrogen or methyl.

In one aspect of the invention R^3 and R^5 together with the carbon atoms to which they are attached form a piperidine ring substituted by methyl.

In one aspect of the invention R^6 is hydrogen or methyl.

In one aspect of the invention R^7 is hydrogen or a group selected from C_{1-6}alkyl, C_{3-7}cycloalkyl, aryl, heteroaryl or heterocyclyl where the group is optionally substituted by heterocyclyl, aryl and heteroaryl; and wherein the group from which R^7 may be selected is optionally substituted on the group and/or on its optional substituent by one or more substitutents independently selected from halo, cyano, C_{1-4}alkyl, $-OR^{21}$, $-CO_2R^{21}$, $-NR^{21}COR^{22}$, $-NR^{21}CO_2R^{22}$ and $-CONR^{21}R^{22}$.

In another aspect R^7 is hydrogen or a group selected from C_{1-4}alkyl, arylC_{1-4}alkyl, heteroarylC_{1-4}alkyl, heterocyclylC_{1-4}alkyl, aryl, heteroaryl, heterocyclyl and C_{3-5}cycloalkyl where the group is optionally substituted by cyano, C_{1-4}alkyl, halo, $-OR^{21}$, $-CO_2R^{21}$ and $-NR^{21}CO_2R^{22}$.

In a further aspect R^7 is selected from hydrogen, methyl, ethyl, propyl, prop-2-yl, butyl, tert-butyl, 2-methylpropyl, 1-hydroxyethyl, 2-hydroxyethyl, 3-hydroxypropyl, 2-cyanoethyl, phenyl, pyridyl, benzyl, 3-methylbenzyl, phenylethyl, 4-chlorophenylethyl, 4-fluorophenylethyl, phenylpropyl, 4-chlorophenylpropyl, 4-fluorophenylpropyl, 4-methylpiperazin-1-ylethyl, morpholin-4-ylpropyl, pyrimidin-2-ylethyl, pyrimidin-2-ylpropyl, pyrimidin-2-ylbutyl, 5-fluoropyrimidin-2-ylpropyl, imidazol-1-ylpropyl, imidazol-1-ylbutyl, 1,2,4-triazolylpropyl, piperidinyl, carbamoylphenyl, tetrahydro-2H-pyranyl, tetrahydro-2H-

pyranylmethyl, pyrid-2-ylmethyl, pyrid-4-ylmethyl, pyrid-3-ylmethyl, piperidin-4-ylmethyl, N-(t-butoxycarbonyl)piperidin-4-yl, , benzyloxyethyl, n-(t-butoxycarbonyl)piperidin-4-ylmethyl, (3,4,4-trimethyl-2,5-dioximidazolidin-1-yl)methyl, and N-benzoyl-N-phenylaminomethyl.

In one aspect of the invention R^3 and R^7 together with the carbon atoms to which they are each attached and $(CR^5R^6)_n$ form a piperidinyl, pyrrolidinyl, piperazine or morpholine ring.

In one aspect R^8 is hydrogen or methyl.

In one aspect R^9 is hydrogen or methyl.

In one aspect R^{10} is hydrogen or methyl.

In one aspect R^{11} is methyl.

In one aspect R^{12} is hydrogen or methyl.

In one aspect R^{13} is hydrogen or methyl.

In one aspect R^{14} is hydrogen, methyl or amino.

In one aspect R^{15} is hydrogen or methyl.

In one aspect R^{16} is hydrogen or methyl.

In one aspect R^{17} is selected from fluoro, chloro, methyl or methoxy.

In one aspect of the invention R^{19} is a group selected from C_{1-6}alkyl, aryl and arylC_{1-4}alkyl where the group is optionally substituted by halo.

In another aspect R^{19} is a group selected from methyl, phenyl and benzyl where the group is optionally substituted by chloro.

In one aspect of the invention R^{19} is methyl.

In one aspect of the invention R^{18} is hydrogen or a group selected from C_{1-6}alkyl, aryl and arylC_{1-4}alkyl where the group is optionally substituted by halo.

In another aspect R^{18} is hydrogen or a group selected from methyl, phenyl and benzyl where the group is optionally substituted by chloro.

In one aspect R^{20} is hydrogen or methyl.

In one aspect R^{21} is hydrogen, methyl, ethyl, phenyl, benzyl and benzoyl.

In one aspect R^{22} is hydrogen, methyl, ethyl, phenyl, benzyl and benzoyl.

In another aspect R^{22} is hydrogen or methyl.

In one aspect R^{23} is hydrogen or methyl.

In one aspect R^{24} is hydrogen or methyl.

In one aspect of the invention R^{25} is a group selected from C_{1-6}alkyl, aryl and arylC_{1-4}alkyl where the group is optionally substituted by halo.

In another aspect R^{25} is a group selected from methyl, phenyl and benzyl where the group is optionally substituted by chloro.

In one aspect of the invention R^{25} is methyl.

A preferred class of compound is of the formula (1) wherein:

Y^1 and Y^2 are both O;

z is NR^8;

n is 0 or 1;

W is NR^1, CR^1R^2 or a bond;

V is a group of formula (A), C(=O), $NR^{15}C(=O)$ or $NR^{15}SO_2$;

t is 0 or 1;

B is a group selected from aryl, heteroaryl and heterocyclyl where each group is optionally substituted by one or more groups independently selected from nitro, trifluoromethyl,

trifluoromethoxy, halo, cyano, C_{1-4}alkyl (optionally substituted by R^9 or one or more halo), C_{2-4}alkenyl (optionally substituted by halo or R^9), C_{2-4}alkynyl (optionally substituted by halo or R^9), C_{3-6}cycloalkyl (optionally substituted by R^9 or one or more halo), C_{5-6}cycloalkenyl (optionally substituted by halo or R^9), aryl (optionally substituted by halo or C_{1-4}alkyl), heteroaryl (optionally substituted by halo or C_{1-4}alkyl), heterocyclyl (optionally substituted by C_{1-4}alkyl), $-SR^{11}$, $-SOR^{11}$, $-SO_2R^{11}$, $-SO_2NR^9R^{11}$, $-NR^9SO_2R^{10}$, $-NHCONR^9R^{10}$, $-OR^9$, $-NR^9R^{10}$, $-CONR^9R^{10}$ and $-NR^9COR^{10}$; or B is C_{2-4}alkenyl or C_{2-4}alkynyl, each being optionally substituted by a group selected from C_{1-4}alkyl, C_{3-6}cycloalkyl, aryl, heteroaryl, heterocyclyl whereby this group is optionally substituted by one or more halo, nitro, cyano, trifluoromethyl, trifluoromethoxy, $-CONHR^9$, $-CONR^9R^{10}$, $-SO_2R^{11}$, $-SO_2NR^9R^{10}$, $-NR^9SO_2R^{11}$, C_{1-4}alkyl and C_{1-4}alkoxy;

R^1 and R^2 are independently hydrogen or methyl;

R^3 is hydrogen, methyl, propyl or phenyl;

R^4, R^5, R^6, R^8, R^9, R^{10}, R^{12}, R^{13} and R^{15} are independently hydrogen or methyl;

R^{11} is methyl;

R^7 is hydrogen or a group selected from C_{1-6}alkyl, C_{3-7}cycloalkyl, aryl, heteroaryl or heterocyclyl where the group is optionally substituted by heterocyclyl, aryl and heteroaryl; and wherein the group from which R^7 may be selected is optionally substituted on the group and/or on its optional substituent by one or more substitutents independently selected from halo, cyano, C_{1-4}alkyl, $-OR^{21}$, $-CO_2R^{21}$, $-NR^{21}COR^{22}$, $-NR^{21}CO_2R^{22}$ and $-CONR^{21}R^{22}$;

R^{14} is hydrogen, methyl or amino; and

R^{21} and R^{22} are independently hydrogen, methyl, ethyl, phenyl, benzyl or benzoyl.

A preferred class of compound is of the formula (1) wherein:

Y^1 and Y^2 are both O;

z is NR^8;

n is 1;

W is NR^1, CR^1R^2 or a bond;

V is SO_2;

t is 0 or 1;

B is a group selected from aryl, heteroaryl and heterocyclyl where each group is optionally substituted by one or more groups independently selected from nitro, trifluoromethyl,

trifluoromethoxy, halo, cyano, C_{1-4}alkyl (optionally substituted by R^9 or one or more halo), C_{2-4}alkenyl (optionally substituted by halo or R^9), C_{2-4}alkynyl (optionally substituted by halo or R^9), C_{3-6}cycloalkyl (optionally substituted by R^9 or one or more halo), C_{5-6}cycloalkenyl (optionally substituted by halo or R^9), aryl (optionally substituted by halo or C_{1-4}alkyl), heteroaryl (optionally substituted by halo or C_{1-4}alkyl), heterocyclyl (optionally substituted by C_{1-4}alkyl), $-SR^{11}$, $-SOR^{11}$, $-SO_2R^{11}$, $-SO_2NR^9R^{11}$, $-NR^9SO_2R^{10}$, $-NHCONR^9R^{10}$, $-OR^9$, $-NR^9R^{10}$, $-CONR^9R^{10}$ and $-NR^9COR^{10}$; or B is C_{2-4}alkenyl or C_{2-4}alkynyl, each being optionally substituted by a group selected from C_{1-4}alkyl, C_{3-6}cycloalkyl, aryl, heteroaryl, heterocyclyl whereby this group is optionally substituted by one or more halo, nitro, cyano, trifluoromethyl, trifluoromethoxy, $-CONHR^9$, $-CONR^9R^{10}$, $-SO_2R^{11}$, $-SO_2NR^9R^{10}$, $-NR^9SO_2R^{11}$, C_{1-4}alkyl and C_{1-4}alkoxy;

R^1 and R^2 are independently hydrogen or methyl;

R^3 is hydrogen, methyl, propyl or phenyl;

R^4, R^5, R^6, R^8, R^9, R^{10}, R^{12} and R^{13} are independently hydrogen or methyl;

R^{11} is methyl;

R^7 is hydrogen or a group selected from C_{1-6}alkyl, C_{3-7}cycloalkyl, aryl, heteroaryl or heterocyclyl where the group is optionally substituted by heterocyclyl, aryl and heteroaryl; and wherein the group from which R^7 may be selected is optionally substituted on the group and/or on its optional substituent by one or more substitutents independently selected from halo, cyano, C_{1-4}alkyl, $-OR^{21}$, $-CO_2R^{21}$, $-NR^{21}COR^{22}$, $-NR^{21}CO_2R^{22}$ and $-CONR^{21}R^{22}$; and

R^{21} and R^{22} are independently hydrogen, methyl, ethyl, phenyl, benzyl or benzoyl.

Another preferred class of compound is of the formula (1) wherein:

Y^1 and Y^2 are both O;

z is NR^8;

n is 0;

W is CR^1R^2;

V is SO_2;

t is 0 or 1;

B is a group selected from aryl, heteroaryl and heterocyclyl where each group is optionally substituted by one or more groups independently selected from nitro, trifluoromethyl,

trifluoromethoxy, halo, cyano, C_{1-4}alkyl (optionally substituted by R^9 or one or more halo), C_{2-4}alkenyl (optionally substituted by halo or R^9), C_{2-4}alkynyl (optionally substituted by halo or R^9), C_{3-6}cycloalkyl (optionally substituted by R^9 or one or more halo), C_{5-6}cycloalkenyl (optionally substituted by halo or R^9), aryl (optionally substituted by halo or C_{1-4}alkyl), heteroaryl (optionally substituted by halo or C_{1-4}alkyl), heterocyclyl (optionally substituted by C_{1-4}alkyl), $-SR^{11}$, $-SOR^{11}$, $-SO_2R^{11}$, $-SO_2NR^9R^{11}$, $-NR^9SO_2R^{10}$, $-NHCONR^9R^{10}$, $-OR^9$, $-NR^9R^{10}$, $-CONR^9R^{10}$ and $-NR^9COR^{10}$; or B is C_{2-4}alkenyl or C_{2-4}alkynyl, each being optionally substituted by a group selected from C_{1-4}alkyl, C_{3-6}cycloalkyl, aryl, heteroaryl, heterocyclyl whereby this group is optionally substituted by one or more halo, nitro, cyano, trifluoromethyl, trifluoromethoxy, $-CONHR^9$, $-CONR^9R^{10}$, $-SO_2R^{11}$, $-SO_2NR^9R^{10}$, $-NR^9SO_2R^{11}$, C_{1-4}alkyl and C_{1-4}alkoxy;

R^1 and R^2 are independently hydrogen or methyl;

R^3 is hydrogen, methyl, propyl or phenyl;

R^4, R^8, R^9, R^{10}, R^{12} and R^{13} are independently hydrogen or methyl;

R^{11} is methyl;

R^7 is hydrogen or a group selected from C_{1-6}alkyl, C_{3-7}cycloalkyl, aryl, heteroaryl or heterocyclyl where the group is optionally substituted by heterocyclyl, aryl and heteroaryl; and wherein the group from which R^7 may be selected is optionally substituted on the group and/or on its optional substituent by one or more substitutents independently selected from halo, cyano, C_{1-4}alkyl, $-OR^{21}$, $-CO_2R^{21}$, $-NR^{21}COR^{22}$, $-NR^{21}CO_2R^{22}$ and $-CONR^{21}R^{22}$; and

R^{21} and R^{22} are independently hydrogen, methyl, ethyl, phenyl, benzyl or benzoyl.

Another preferred class of compound is of the formula (1) wherein:

Y^1 and Y^2 are both O;

z is NR^8;

n is 0;

W is NR^1 or a bond;

V is SO_2;

t is 0 or 1;

B is a group selected from bicyclic aryl, bicyclic heteroaryl and bicyclic heterocyclyl, where each group is optionally substituted by one or more groups independently selected from nitro, trifluoromethyl, trifluoromethoxy, halo, cyano, C_{1-4}alkyl (optionally substituted by R^9 or one

or more halo), C_{2-4}alkenyl (optionally substituted by halo or R^9), C_{2-4}alkynyl (optionally substituted by halo or R^9), C_{3-6}cycloalkyl (optionally substituted by R^9 or one or more halo), C_{5-6}cycloalkenyl (optionally substituted by halo or R^9), aryl (optionally substituted by halo or C_{1-4}alkyl), heteroaryl (optionally substituted by halo or C_{1-4}alkyl), heterocyclyl (optionally substituted by C_{1-4}alkyl), $-SR^{11}$, $-SOR^{11}$, $-SO_2R^{11}$, $-SO_2NR^9R^{10}$, $-NR^9SO_2R^{11}$, $-NHCONR^9R^{10}$, $-OR^9$, $-NR^9R^{10}$, $-CONR^9R^{10}$ and $-NR^9COR^{10}$; or B is C_{2-4}alkenyl or C_{2-4}alkynyl, each being optionally substituted by a group selected from C_{1-4}alkyl, C_{3-6}cycloalkyl, aryl, heteroaryl, heterocyclyl whereby this group is optionally substituted by one or more halo, nitro, cyano, trifluoromethyl, trifluoromethoxy, $-CONHR^9$, $-CONR^9R^{10}$, $-SO_2R^{11}$, $-SO_2NR^9R^{10}$, $-NR^9SO_2R^{11}$, C_{1-4}alkyl and C_{1-4}alkoxy;

R^1 is hydrogen or methyl;

R^3 is hydrogen, methyl, propyl or phenyl;

R^4, R^8, R^9, R^{10}, R^{12} and R^{13} are independently hydrogen or methyl;

R^{11} is methyl;

R^7 is hydrogen or a group selected from C_{1-6}alkyl, C_{3-7}cycloalkyl, aryl, heteroaryl or heterocyclyl where the group is optionally substituted by heterocyclyl, aryl and heteroaryl; and wherein the group from which R^7 may be selected is optionally substituted on the group and/or on its optional substituent by one or more substitutents independently selected from halo, cyano, C_{1-4}alkyl, $-OR^{21}$, $-CO_2R^{21}$, $-NR^{21}COR^{22}$, $-NR^{21}CO_2R^{22}$ and $-CONR^{21}R^{22}$; and

R^{21} and R^{22} are independently hydrogen, methyl, ethyl, phenyl, benzyl or benzoyl.

Another preferred class of compound is of the formula (1) wherein:

Y^1 and Y^2 are both O;

z is NR^8;

n is 0;

W is NR^1 or a bond;

V is SO_2;

t is 0 or 1;

B is a group selected from aryl and heteroaryl where each group is optionally substituted by one or more groups independently selected from halo, C_{1-4}alkyl (optionally substituted by one or more halo), C_{2-4}alkenyl (optionally substituted by halo) and C_{2-4}alkynyl (optionally substituted by halo); or B is C_{2-4}alkenyl or C_{2-4}alkynyl, each being optionally substituted by a

group selected from C_{1-4}alkyl, C_{3-6}cycloalkyl, aryl, heteroaryl, heterocyclyl whereby this group is optionally substituted by one or more halo, nitro, cyano, trifluoromethyl, trifluoromethoxy, $-CONHR^9$, $-CONR^9R^{10}$, $-SO_2R^{11}$, $-SO_2NR^9R^{10}$, $-NR^9SO_2R^{11}$, C_{1-4}alkyl and C_{1-4}alkoxy; provided that when t is 0 and B is monocyclic aryl or monocyclic heteroaryl then the monocyclic group that is B is substituted on the carbon or nitrogen adjacent to the atom to which the oxygen is attached, by a group described above

R^1 is hydrogen or methyl;

R^3 is hydrogen, methyl, propyl or phenyl;

R^4, R^8, R^9, R^{10}, R^{12} and R^{13} are independently hydrogen or methyl;

R^{11} is methyl;

R^7 is hydrogen or a group selected from C_{1-6}alkyl, C_{3-7}cycloalkyl, aryl, heteroaryl or heterocyclyl where the group is optionally substituted by heterocyclyl, aryl and heteroaryl; and wherein the group from which R^7 may be selected is optionally substituted on the group and/or on its optional substituent by one or more substitutents independently selected from halo, cyano, C_{1-4}alkyl, $-OR^{21}$, $-CO_2R^{21}$, $-NR^{21}COR^{22}$, $-NR^{21}CO_2R^{22}$ and $-CONR^{21}R^{22}$; and

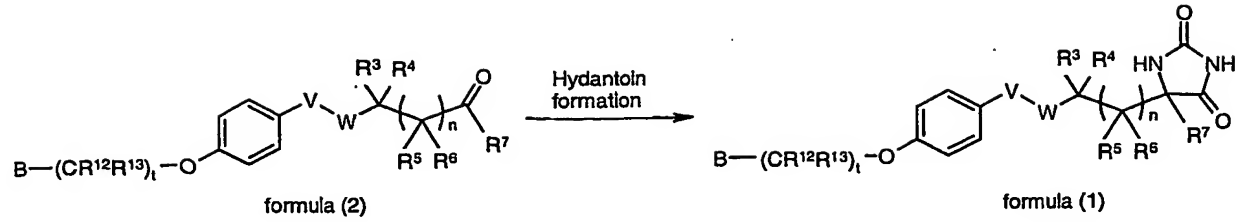
R^{21} and R^{22} are independently hydrogen, methyl, ethyl, phenyl, benzyl and benzoyl..

In another aspect of the invention, preferred compounds of the invention are any one of:

5-{3-Methyl-3-[4-(2-methyl-quinolin-4-ylmethoxy)-phenyl]-2-oxo-pyrrolidin-1-ylmethyl}-imidazolidine-2,4-dione; and

5-(1-{3-Methyl-3-[4-(2-methyl-quinolin-4-ylmethoxy)-phenyl]-2-oxo-pyrrolidin-1-yl}-ethyl)-imidazolidine-2,4-dione.

In another aspect the present invention provides a process for the preparation of a compound of formula (1) or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof wherein Y^1 and Y^2 are both O, z is NR^8 and R^8 is hydrogen, which comprises converting a ketone or aldehyde of formula (2) into a compound of formula (1);



Scheme 1

and thereafter if necessary:

i) converting a compound of the formula (1) into another compound of the formula (1);

ii) removing any protecting groups;

iii) forming a pharmaceutically acceptable salt or *in vivo* hydrolysable ester.

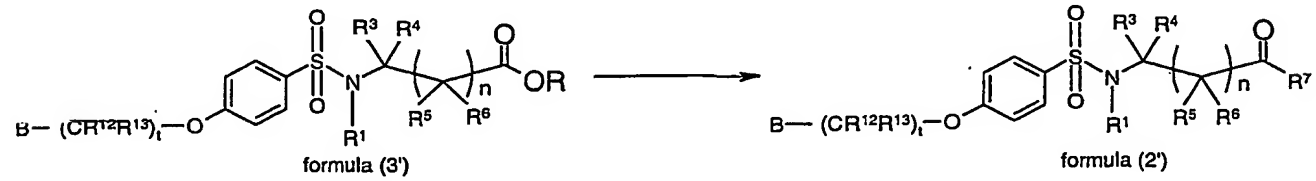
The hydanoin can be prepared by a number of methods for example;

a) The aldehyde or ketone may be reacted with ammonium carbonate and potassium cyanide in aqueous alcohols using the method of Bucherer and Bergs (*Adv. Het. Chem.*, 1985, **38**, 177).

b) The aldehyde or ketone could be first converted to the cyanohydrin and then further reacted with ammonium carbonate (*Chem. Rev*, 1950, **56**, 403).

c) The aldehyde or ketone could be converted to the alpha-amino nitrile and then either reacted with ammonium carbonate or aqueous carbon dioxide or potassium cyanate followed by mineral acid (*Chem. Rev*, 1950, **56**, 403).

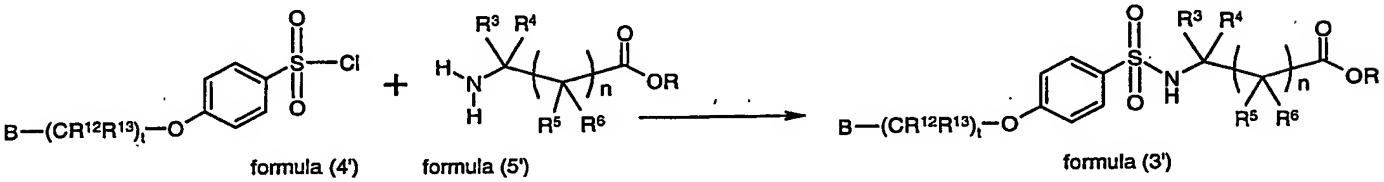
The process may further comprise a process for the preparation of a ketone or aldehyde of formula (2) wherein V is SO_2, and W is NR^1 (indicated as a compound of formula (2')) which process comprises converting an ester of formula (3') (where R is C_{1-10}alkyl) into an aldehyde or ketone of formula (2');



Scheme 2

Suitable reagents for such a transformation are Grignard reagents to prepare ketones or diisobutylaluminium hydride in dichloromethane at –78°C under an argon atmosphere to prepare aldehydes.

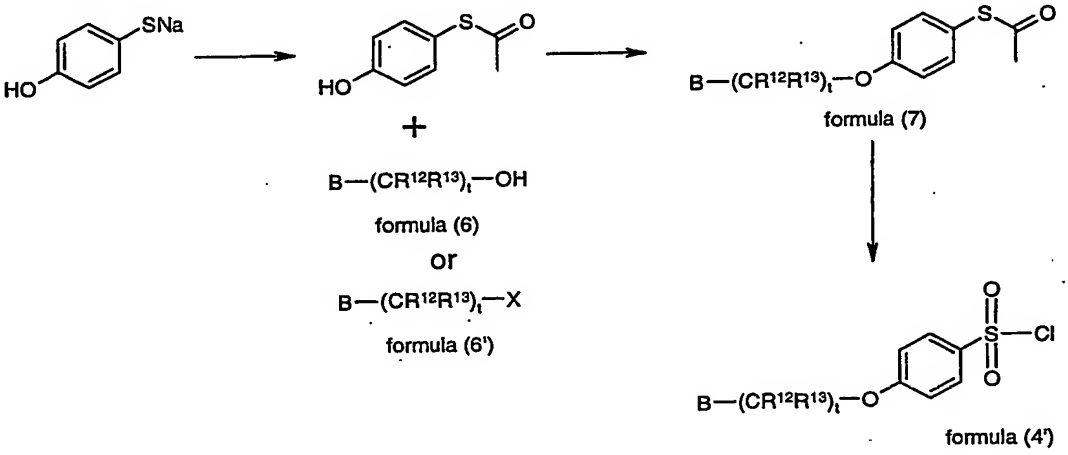
The ester of formula (3') can be prepared by reaction of a compound of formula (4') with a compound of formula (5') or its salt under standard sulphonamide formation conditions (e.g. triethylamine in DCM at temperatures from 0°C to 50°C);



Scheme 3

Many compounds of formula (5') are commercially available.

The sulphonyl chloride of formula (4') can be prepared as outlined in Scheme 4 which comprises;



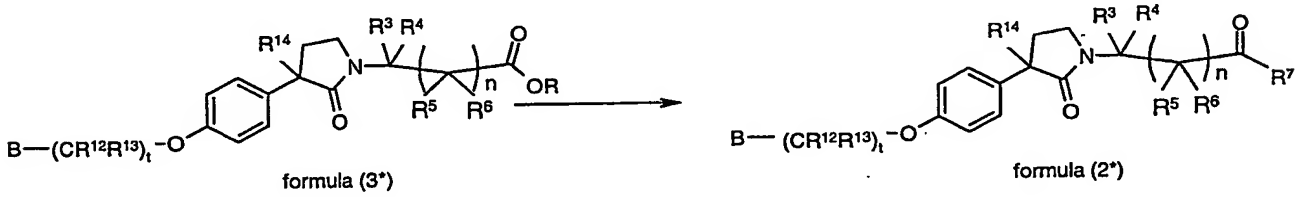
Scheme 4

a) reacting the monosodium salt of 4-mercaptophenol with acetic anhydride (*J. Am. Chem. Soc.*, 1956, **78**, 854.) to yield S-(4-hydroxyphenyl)ethanethioate;

b) reacting S-(4-hydroxyphenyl)ethanethioate with an alcohol of formula (6) under Mitsunobu type conditions or by reaction of S-(4-hydroxyphenyl)ethanethioate with a halide of formula (6') by deprotonation with a base such as sodium hydride, LHMDS or caesium carbonate in a solvent such as DMF, THF or DMSO at 0°C to 100°C to give a compound of formula (7); and

c) oxidising a compound of formula (7) by bubbling chlorine gas into a solution of the thiol ester in glacial acetic acid at temperatures from 0°C to room temperature to yield the sulphonyl chloride of formula (4').

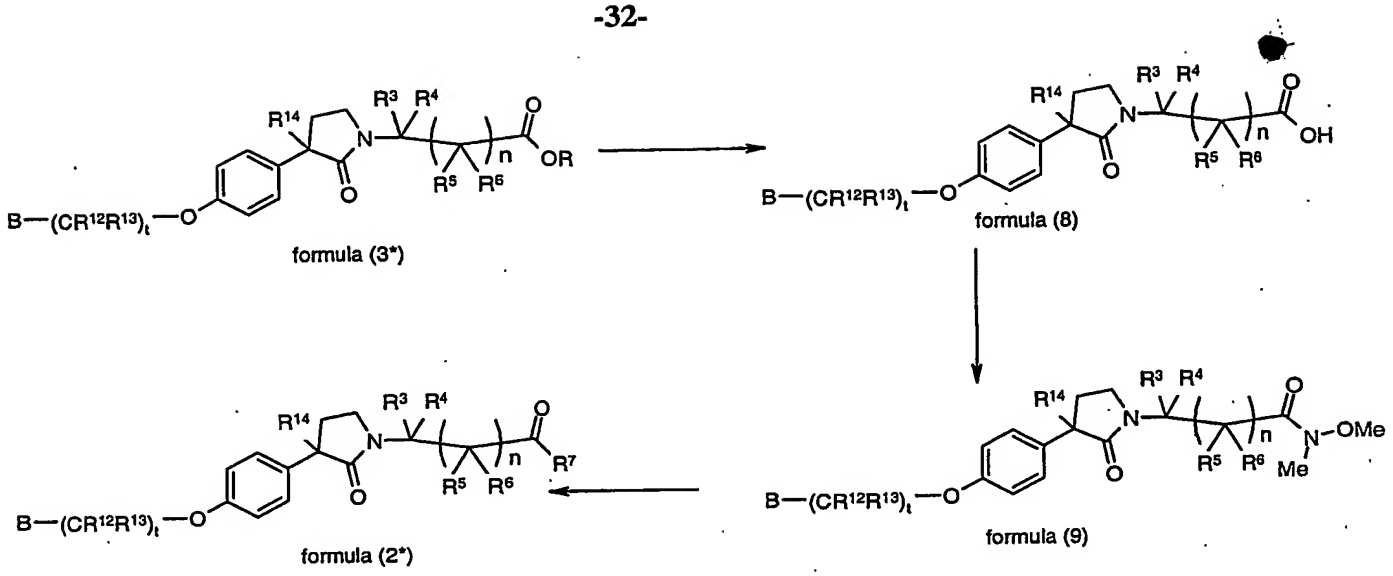
Alternatively a process for the preparation of a ketone or aldehyde of formula (2) where V is a group of formula A and W is a bond (indicated as a compound of formula (2*)) comprises converting an ester of formula (3*) (where R is C_{1-10}alkyl) into a ketone or aldehyde of formula (2*).



Scheme 5

Suitable reagents for such a transformation are Grignard reagents to prepare ketones or diisobutylaluminium hydride in dichloromethane at –78°C under an argon atmosphere to prepare aldehydes.

Alternatively the aldehyde or ketone of formula (2*) may be prepared by the route shown in Scheme 6 which comprises:



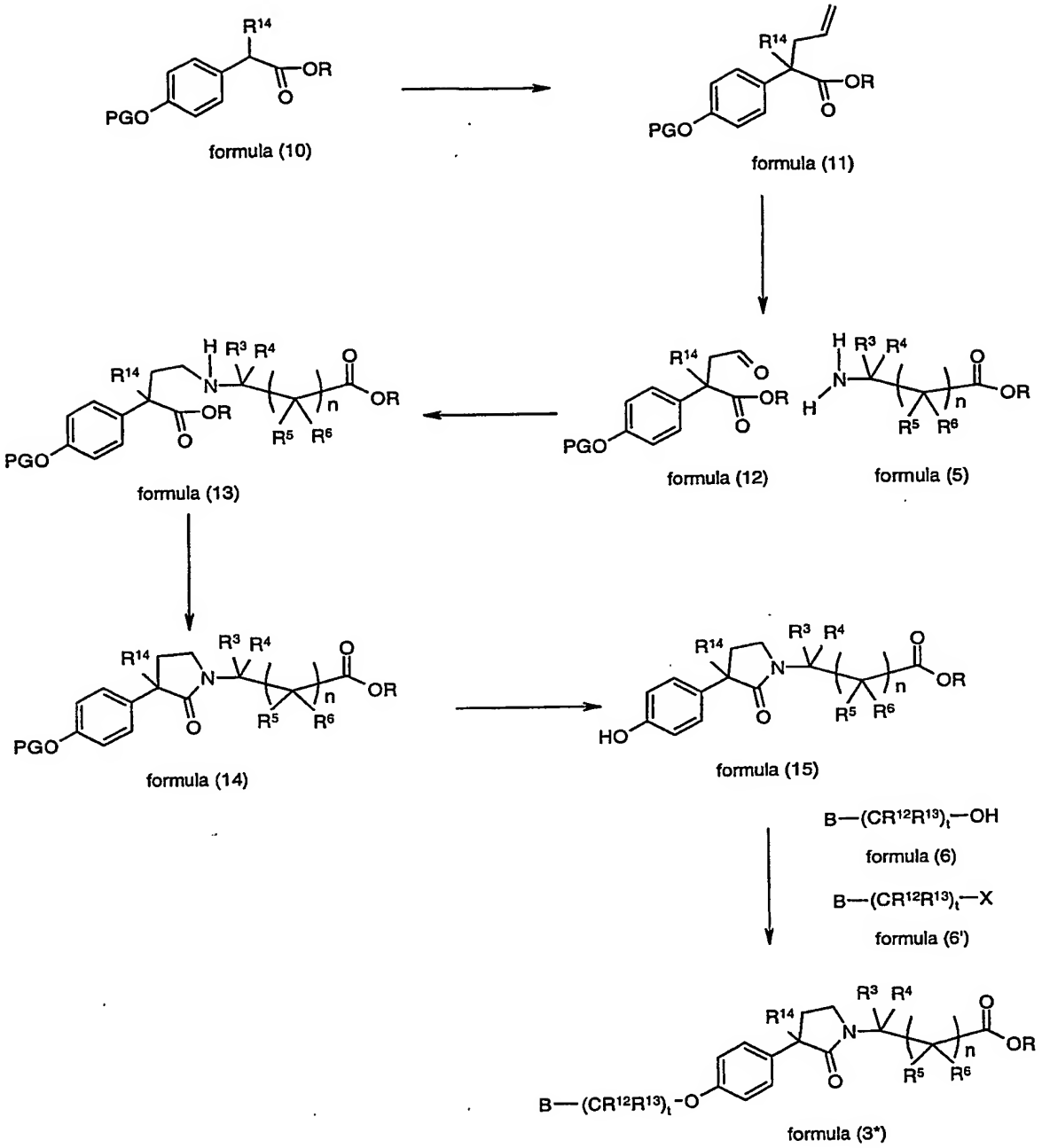
Scheme 6

a) reacting the ester of formula (3*) with a base such as NaOH, KOH or potassium carbonate in alcohols or aqueous alcohols at room temperature to 100°C followed by neutralisation with e.g. acetic acid, to give an acid of formula (8);

b) reacting the acid of formula (8) with N, O-dimethlyhydroxylamine hydrochloride under standard amide coupling conditions or by reacting with triphenylphosphine, carbon tetrabromide and triethylamine in dichlormethane for 10 to 60 minutes (Synth. Commun., 1990, **20**, 1105), to give an amide of formula (9); and

c) reacting the amide of formula (9) with a reducing agent such as DIBAL or lithium aluminium hydride to give an aldehyde of formula (2*) or reacting with Grignard reagents to give a ketone of formula (2*).

The ester of formula (3*) may be prepared as shown in Scheme 7;



Scheme 7

The process of Scheme 7 comprises the steps of:

a) reacting an ester of formula (10), where PG is a protecting group such as benzyl and R is C_{1-10}alkyl, with a base such LDA or LHMDS in THF at a temperature of –78°C to 0°C followed by reaction with allyl bromide for 30 min to 2 h to give an allylated product of formula (11);

b) reacting the allylated product of formula (11) with ozone, until no more starting compound can be observed by tlc or hplc/ms followed by reduction of the resultant ozonide with e.g. dimethylsulphide, triphenylphosphine or polymer supported triphenylphosphine to give an aldehyde of formula (12);

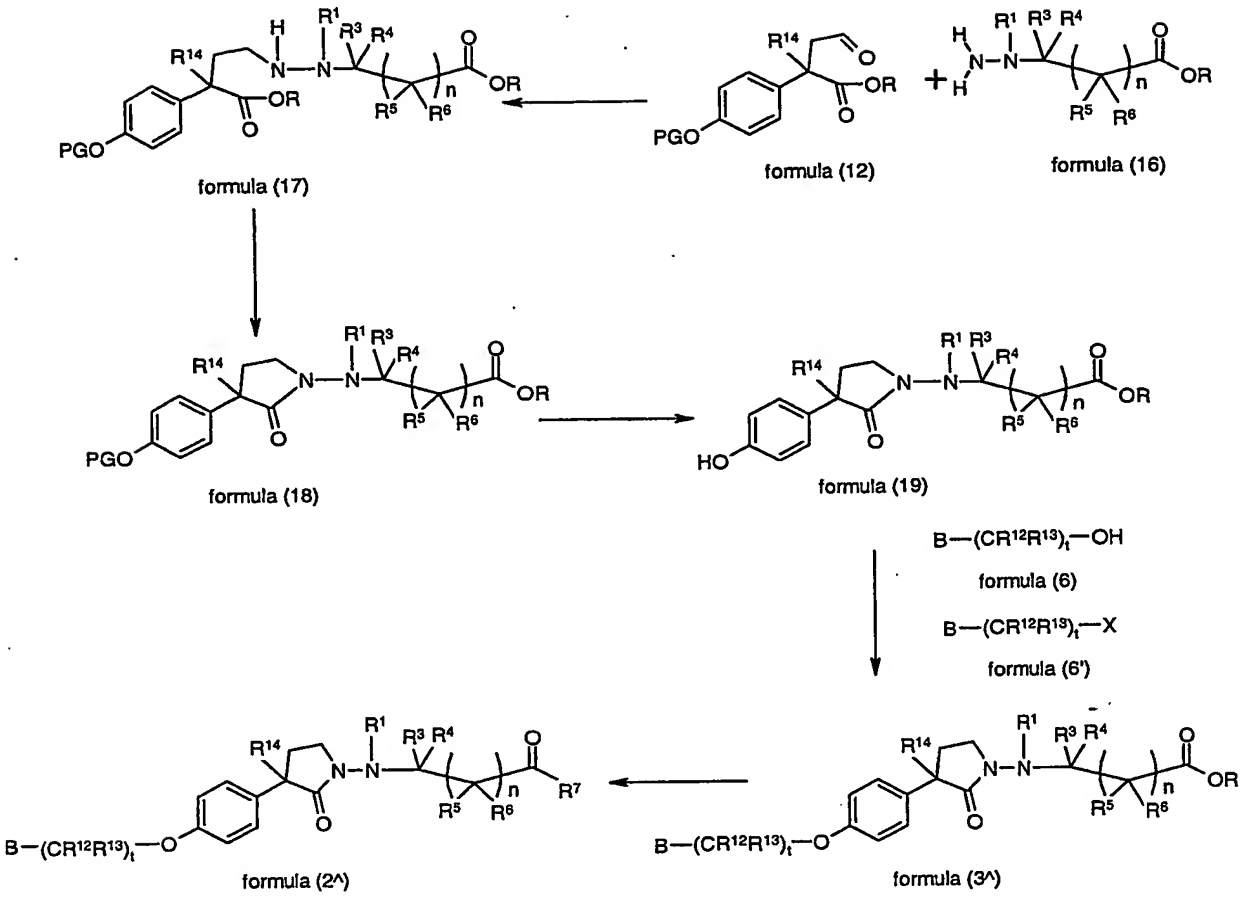
c) reacting the aldehyde of formula (12) with an amine or amine salt of formula (5) (where R is C_{1-10}alkyl) in a solvent such as DCM or DCE in the presence of a base such as TEA or DIPEA for 30min to 2h before addition of a reducing agent such as sodium triacetoxyborohydride, sodium borohydride or sodium cyanoborohydride and reacted at room temperature for 2 to 24 h. to give an amine of formula (13);

d) cyclisation of the amine of formula (13) by heating in an inert solvent such as toluene to 90-110°C for 1 to 4 h to give a lactam of formula (14);

e) removal of the protecting group to give a phenol of formula (15) (if a benzyl protecting group is used this can be removed by treatment with palladium on carbon in the presence of either hydrogen of cyclohexene);

f) reacting the phenol of formula (15) with an alcohol of formula (6) under Mitsunobu type conditions or by reaction of the phenol with a halide of formula (6') by deprotonation with a base such as NaH, LHMDS in a solvent such as DMF or THF at 0°C to 100°C or deprotonation with caesium carbonate in the presence of tetrabutyl ammonium iodide in DMSO at room temperature to 100°C to give a compound of formula (3*).

Alternatively a process for the preparation of a ketone or aldehyde of formula (2) where V is a group of formula A and W is NR^1 (indicated as a compound of formula (2^)) comprises:



Scheme 8

a) reacting an aldehyde of formula (12) with an hydrazine or hydrazine salt of formula (16) in a solvent such as DCM or DCE in the presence of a base such as TEA or DIPEA for 30min to 2h before addition of a reducing agent such as sodium triacetoxyborohydride, sodium borohydride or sodium cyanoborohydride and reacted at room temperature for 2 to 24 h to give a hydrazine of formula (17);

b) cyclisation of the hydrazine of formula (17) by heating in an inert solvent such as toluene to 90-110°C for 1 to 4 h to give a lactam of formula (18);

c) removal of the protecting group to give a phenol of formula (19) (if a benzyl protecting group is used this can be removed by treatment with palladium on carbon in the presence of either hydrogen of cyclohexene);

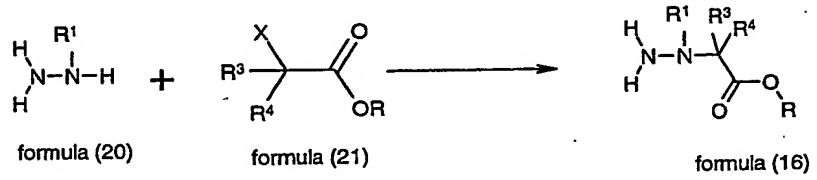
d) reacting the phenol of formula (19) with an alcohol of formula (6) under Mitsunobu type conditions or by reaction of the phenol with a halide of formula (6') by deprotonation with a base such as NaH, LHMDS in a solvent such as DMF

or THF at 0°C to 100°C or deprotonation with caesium carbonate in the presence of tetrabutyl ammonium iodide in DMSO at room temperature to 100°C to give a compound of formula (3^);

e) converting the ester of formula (3^) to an aldehyde or ketone of formula (2^).

Suitable reagents for the transformation of e) are Grignard reagents to prepare ketones or diisobutylaluminium hydride in dichloromethane at –78°C under an argon atmosphere to prepare aldehydes.

The hydrazine of formula (16) when n is 0 or its salt can be prepared by reaction of a hydrazine of formula (20) with an alpha-halo ester of formula (21) in the presence of a base such as sodium methoxide in an inert solvent e.g. DCM at a temperature of room temperature to reflux.

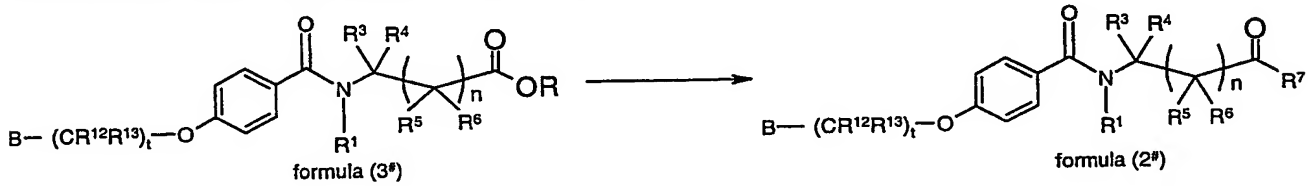


formula (20) formula (21) formula (16)

Scheme 9

For the hydrazine of formula (16) when n is 1, a beta-halo ester should be used in place of the alpha-halo ester in Scheme 9.

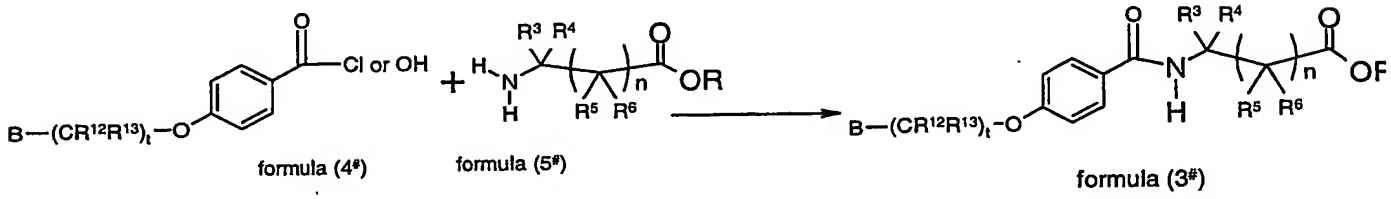
Alternatively a process for the preparation of a ketone or aldehyde of formula (2) where V is C(=O), W is NR^1 and R^1 is hydrogen (indicated as a compound of formula ($2^{\#}$)) comprises converting an ester of formula ($3^{\#}$) into an aldehyde or ketone of formula ($2^{\#}$).



formula ($3^{\#}$) formula ($2^{\#}$)

Scheme 10

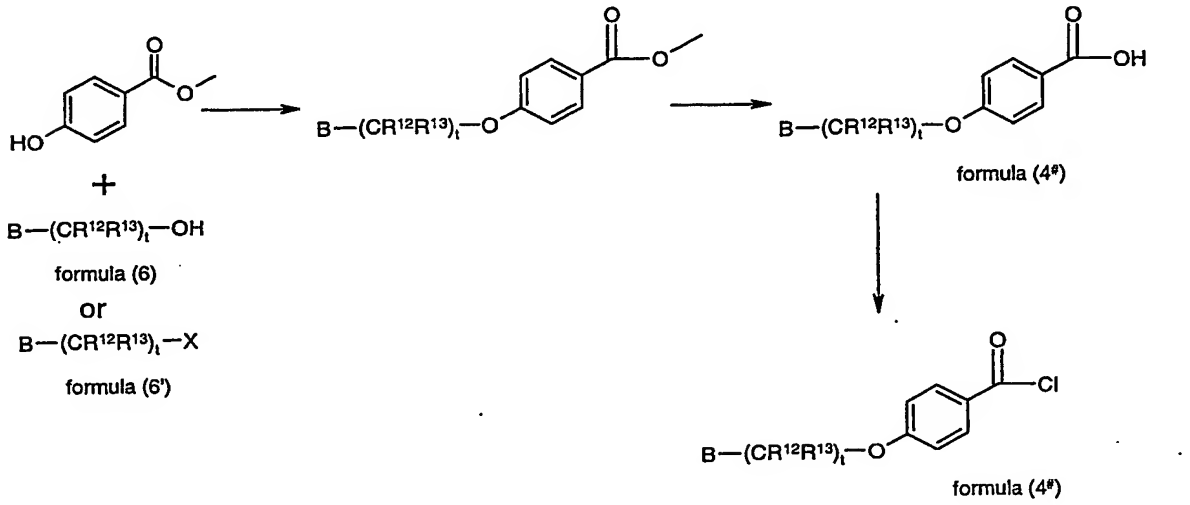
The ester of formula ($3^{\#}$) can be prepared by reaction of a compound of formula ($4^{\#}$) with a compound of formula ($5^{\#}$) or its salt under standard amide formation conditions (e.g. triethylamine in DCM at temperatures from 0°C to 50°C). In addition the carboxylic acid derivative of formula ($4^{\#}$) could used in place of the acid chloride, in which case a coupling agent such as HATU, CDI or EDAC could be used (see Scheme 11).



Scheme 11

Many compounds of formula ($5^{\#}$) are commercially available.

The acid chloride or acid of formula ($4^{\#}$) can be prepared as outlined in Scheme 12:



Scheme 12

The process of Scheme 12 comprises the steps of:

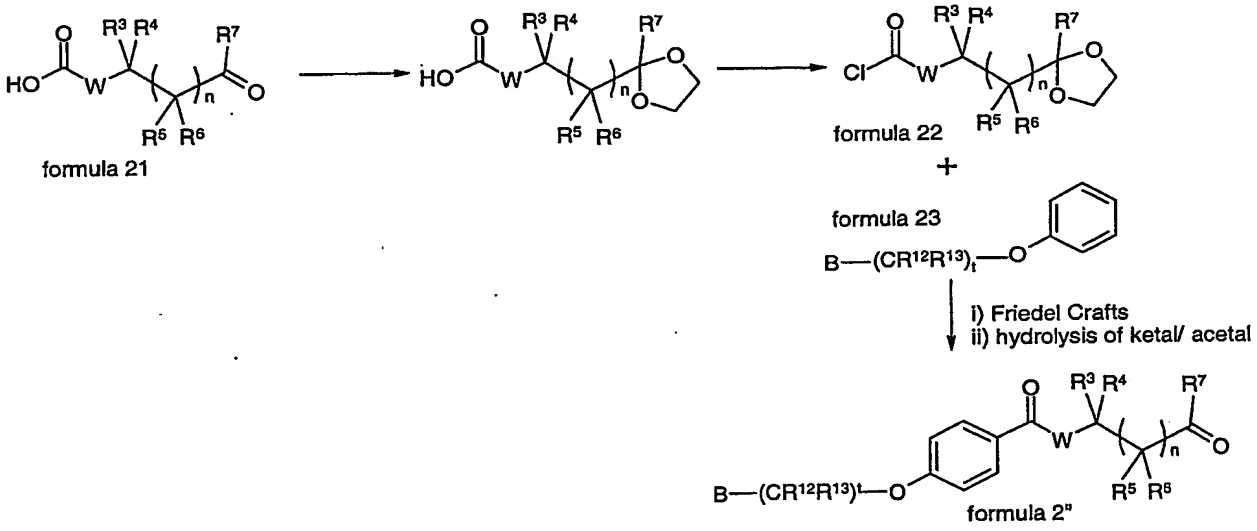
a) reacting methyl 4-hydroxybenzoate with an alcohol of formula (6) under Mitsunobu type conditions or by reaction of methyl 4-hydroxybenzoate with a

halide of formula (6') by deprotonation with a base such as potassium carbonate, sodium hydride, LHMDS or caesium carbonate in a solvent such as acetone, DMF, THF or DMSO at 0°C to 100°C to give an ester;

b) hydrolysing the ester to the acid of formula ($4^{\#}$) using, for example, lithium hydroxide or sodium hydroxide in water at 0°C to 100°C; then

c) the acid of formula ($4^{\#}$) can either be used directly or transformed into the acid chloride of formula ($4^{\#}$) using, for example, oxalyl chloride in DCM at -50°C to RT.

Alternatively a process for the preparation of a ketone or aldehyde of formula (2) where V is C=O and W is CR^1R^2 or a bond (indicated as a compound of formula (2")) comprises:



Scheme 13

a) protecting a ketone or aldehyde of formula 21 via the ketal/ acetal with 1,2-ethanediol and *p*-toluenesulphonic acid;

b) forming the acid chloride of formula 22 using oxalyl chloride in DCM;

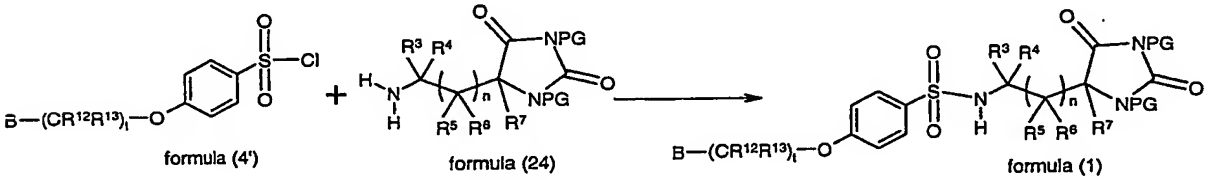
c) Friedel-Crafts acylation of an arylether of formula 23 using the acid chloride and aluminium trichloride in DCM; and

d) hydrolysis of the ketal/ acetal using aqueous HCl or TFA to yield a ketone or aldehyde of formula 2".

The ketone or aldehyde of formula (2") could then be converted to the hydantoin as described above.

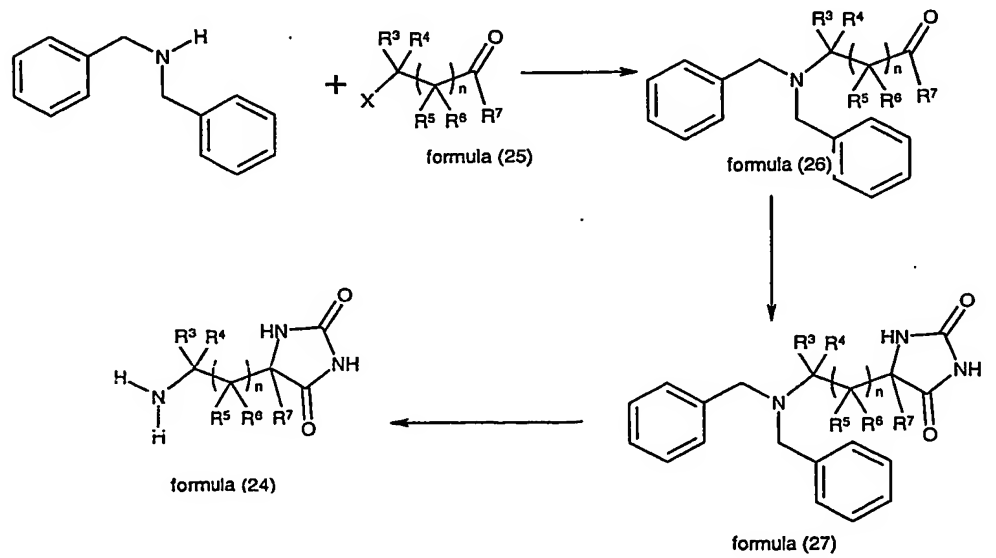
The arylether of this preparation can be prepared by reacting phenol with $B(CR^{12}R^{13})_t$-LG, where LG is a leaving group such as bromide, chloride, mesylate, tosylate or iodide in the presence of a base such as sodium hydride or LiHMDS.

In another aspect the present invention provides a process for the preparation of a compound of formula (1) or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester wherein V is SO_2, W is NR^1 and R^1 is hydrogen, which process comprises coupling a sulphonyl chloride of formula (4') with a hydantoin of formula (24) under standard sulphonamide formation conditions.



Scheme 14

Also provided is a process for the preparation of a hydantion of formula (5^) as shown in Scheme 15 which comprises:

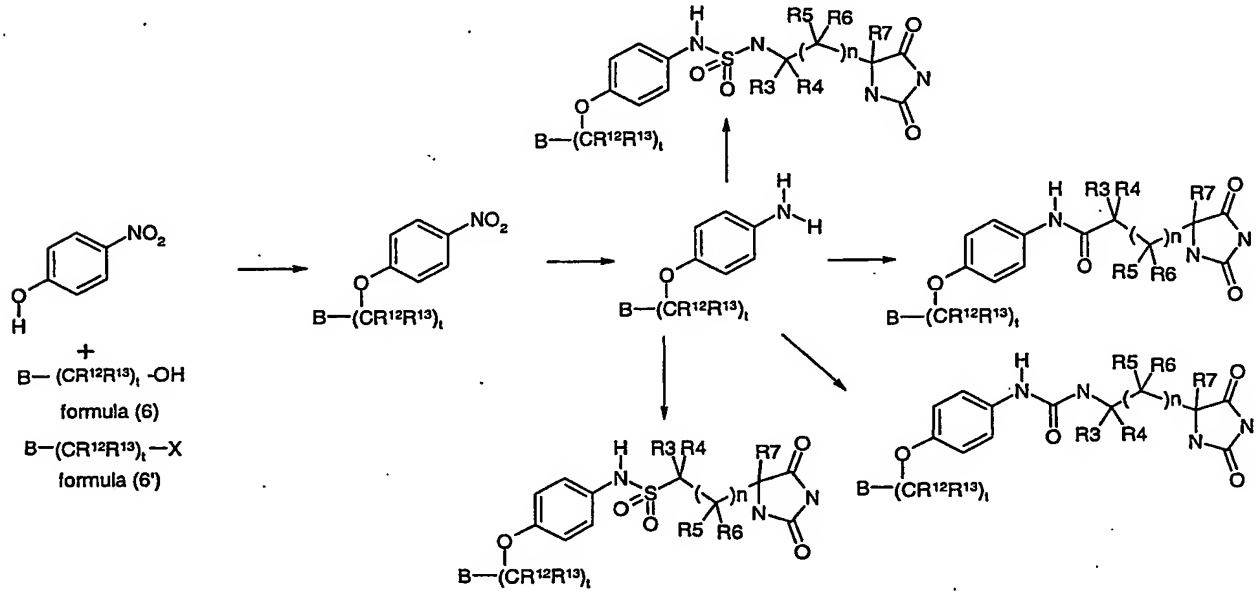


a) reacting dibenzylamine with a halo ketone or aldehyde of formula (25) in an inert solvent such as THF or DCM in the presence of a base e.g TEA at room temperature for 24h to give a protected amino ketone or aldehyde of formula (26);

b) reaction of the ketone or aldehyde under hydantion formation conditions to give a hydontoin of formula (27); and

c) removal of the benzyl protecting groups by reaction with palladium/hydrogen to yield a hydantoin of formula (24).

There is also provided a process for the preparation of a compound of formula 1 where V is $NR^{15}C(=O)$- or $NR^{15}SO_2$- and W is NR_1 or a bond, which process comprises:



Scheme 16

a) alkylating 4-nitrophenol with a compound of formula (6') where X is a leaving group (e.g. –Cl, -Br, -OMs) by deprotonation with a base such as sodium hydride, LHMDS or caesium carbonate in a solvent such as DMF, THF or DMSO at 0°C to 100°C or a Mitsunobu reaction with a compound of formula (6);

b) reduction of the nitro group using e.g. Zn/ HCl or $SnCl_2$/ HCl;

c) sulphamide formation (when W is NR^1) by reaction with SO_2Cl_2 in DCM at temperatures from -78°C to RT to form a chlorosulphonamide intermediate followed

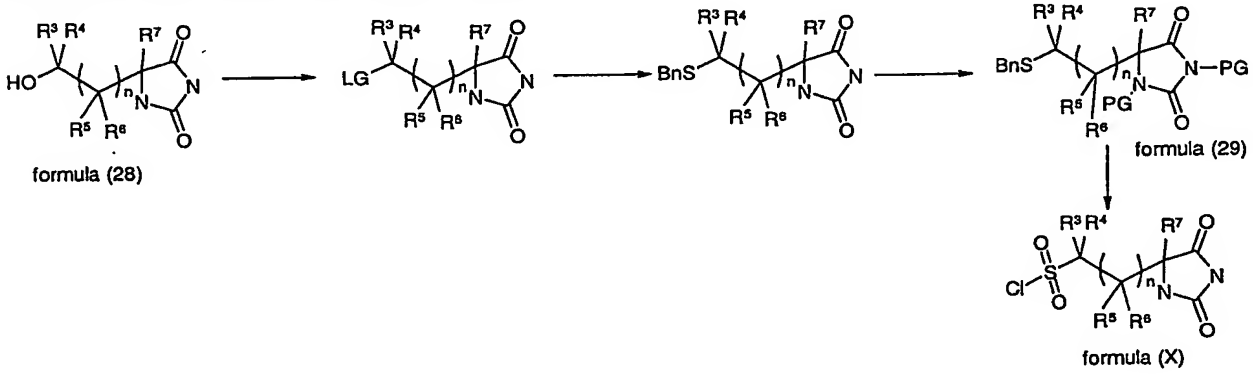
by addition of an amine of formula 24 using standard sulphonamide formation conditions, e.g. in DCM with triethylamine;

d) sulphonamide formation (W is a bond) by addition of a hydantoin sulphonyl chloride of formula (X) using standard sulphonamide formation conditions, e.g. in DCM with triethylamine;

e) amide formation (W is a bond) by addition of a hydantoin carboxylic acid of formula (Y) using standard amide formation conditions, e.g. using EDAC, CDI or HATU in DCM along with dimethylaminopyridine;

f) Urea formation (W is NR^1) by addition of triphosgene in DCM to form an intermediate carbamoyl chloride followed by addition of an amine of formula (24) with triethylamine.

An amine of formula (24) has already been described (see Scheme 14). A sulphonyl chloride of formula (X) can be formed as follows:



Scheme 17

The process of Scheme 17 comprises the steps of:

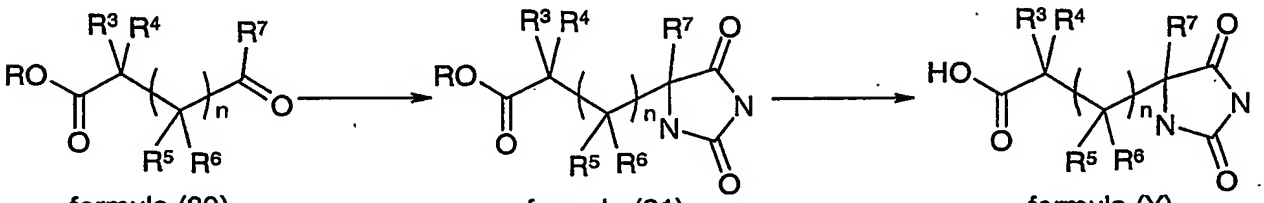
a) transforming the hydroxy hydantoin of formula (28) (which can be prepared by standard methods from aldehydes and ketones as described above) into a leaving group (LG) using, for example, tosyl chloride, mesyl chloride in DCM with triethylamine;

b) displacing the LG using the anion of benzylthiol (deprotonated using NaH) in THF;

c) protecting the hydantoin with a protecting group e.g. benzyl using benzyl bromide and sodium hydride in THF; and

d) treating the benzylthioether of formula (29) with chlorine gas in aqueous acetic acid to yield the sulphonyl chloride of formula (X).

An acid of formula (Y) can be formed as follows:



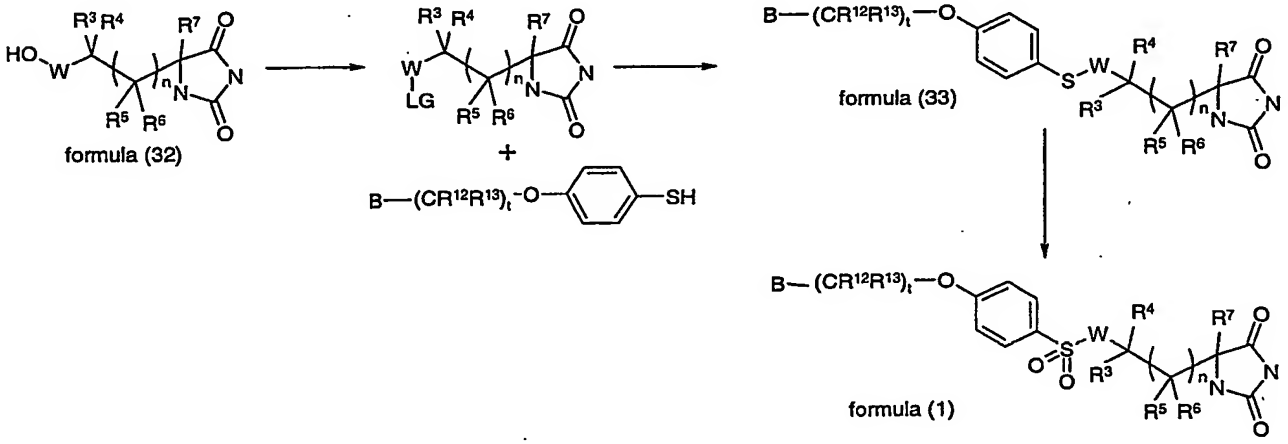
Scheme 18

The process of Scheme 18 comprises the steps of:

a) reacting the aldehyde or ketone of formula (30) with ammonium carbonate and potassium cyanide in aqueous alcohols to give the hydantoin or formula (31);

b) hydrolysing the ester (where R is $C_{1\text{-}10}$alkyl) with aqueous lithium or sodium hydroxide to give the acid of formula (Y).

Further provided is a process for the preparation of a compound of formula (1) where V is SO_2 and W is a bond or CR^1R^2 which process comprises:



Scheme 19

a) transforming the hydroxy hydantoin of formula (32) (which can be prepared by standard methods from aldehydes and ketones as described above) into a leaving group (LG) using, for example, tosyl chloride, mesyl chloride in DCM with triethylamine;

b) displacing the LG with the anion of benzenethiol (deprotonated using NaH) in THF; and

c) oxidising the thioether of formula (33) to the sulphone using, for example mCPBA in DCM.

A compound of formula (1) can be prepared by removal of protecting groups on the hydantoin directly. The protecting group can be *tertiary*-butyloxycarbonyl (BOC), benzyl (Bn) or benzyloxycarbonyl (cbz). These can be removed by treatment with TFA or HCl in dioxane for the former or by treatment with palladium/hydrogen for the latter two.

It will be appreciated that certain of the various ring substituents in the compounds of the present invention may be introduced by standard aromatic substitution reactions or generated by conventional functional group modifications either prior to or immediately following the processes mentioned above, and as such are included in the process aspect of the invention. Such reactions and modifications include, for example, introduction of a substituent by means of an aromatic substitution reaction, reduction of substituents, alkylation of substituents and oxidation of substituents. The reagents and reaction conditions for such procedures are well known in the chemical art. Particular examples of aromatic substitution reactions include the introduction of a nitro group using concentrated nitric acid, the introduction of an acyl group using, for example, an acyl halide and Lewis acid (such as aluminium trichloride) under Friedel Crafts conditions; the introduction of an alkyl group using an alkyl halide and Lewis acid (such as aluminium trichloride) under Friedel Crafts conditions; and the introduction of a halogen group. Particular examples of modifications include the reduction of a nitro group to an amino group by for example, catalytic hydrogenation with a nickel catalyst or treatment with iron in the presence of hydrochloric acid with heating; oxidation of alkylthio to alkylsulphinyl or alkylsulphonyl.

It will also be appreciated that in some of the reactions mentioned herein it may be necessary/desirable to protect any sensitive groups in the compounds. The instances where protection is necessary or desirable and suitable methods for protection are known to those

skilled in the art. Conventional protecting groups may be used in accordance with standard practice (for illustration see T.W. Green, Protective Groups in Organic Synthesis, John Wiley and Sons, 1991). Thus, if reactants include groups such as amino, carboxy or hydroxy it may be desirable to protect the group in some of the reactions mentioned herein.

A suitable protecting group for an amino or alkylamino group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an alkoxycarbonyl group, for example a methoxycarbonyl, ethoxycarbonyl or *t*-butoxycarbonyl group, an arylmethoxycarbonyl group, for example benzyloxycarbonyl, or an aroyl group, for example benzoyl. The deprotection conditions for the above protecting groups necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or alkoxycarbonyl group or an aroyl group may be removed for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively an acyl group such as a *t*-butoxycarbonyl group may be removed, for example, by treatment with a suitable acid as hydrochloric, sulphuric or phosphoric acid or trifluoroacetic acid and an arylmethoxycarbonyl group such as a benzyloxycarbonyl group may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon, or by treatment with a Lewis acid for example boron tris(trifluoroacetate). A suitable alternative protecting group for a primary amino group is, for example, a phthaloyl group which may be removed by treatment with an alkylamine, for example dimethylaminopropylamine, or with hydrazine.

A suitable protecting group for a hydroxy group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an aroyl group, for example benzoyl, or an arylmethyl group, for example benzyl. The deprotection conditions for the above protecting groups will necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or an aroyl group may be removed, for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively an arylmethyl group such as a benzyl group may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon.

A suitable protecting group for a carboxy group is, for example, an esterifying group, for example a methyl or an ethyl group which may be removed, for example, by hydrolysis with a base such as sodium hydroxide, or for example a *t*-butyl group which may be removed, for example, by treatment with an acid, for example an organic acid such as trifluoroacetic

acid, or for example a benzyl group which may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon.

The protecting groups may be removed at any convenient stage in the synthesis using conventional techniques well known in the chemical art.

As stated hereinbefore the compounds defined in the present invention possesses metalloproteinases inhibitory activity, and in particular TACE inhibitory activity. This property may be assessed, for example, using the procedure set out below.

Isolated Enzyme Assays

Matrix Metalloproteinase family including for example MMP13.

Recombinant human proMMP13 may be expressed and purified as described by Knauper *et al.* [V. Knauper *et al.*, (1996) The Biochemical Journal 271:1544-1550 (1996)]. The purified enzyme can be used to monitor inhibitors of activity as follows: purified proMMP13 is activated using 1mM amino phenyl mercuric acid (APMA), 20 hours at 21°C; the activated MMP13 (11.25ng per assay) is incubated for 4-5 hours at 35°C in assay buffer (0.1M Tris-HCl, pH 7.5 containing 0.1M NaCl, 20mM CaCl2, 0.02 mM ZnCl and 0.05% (w/v) Brij 35 using the synthetic substrate 7-methoxycoumarin-4-yl)acetyl.Pro.Leu.Gly.Leu.N-3-(2,4-dinitrophenyl)-L-2,3-diaminopropionyl.Ala.Arg.NH_2 in the presence or absence of inhibitors. Activity is determined by measuring the fluorescence at λex 328nm and λem 393nm. Percent inhibition is calculated as follows: % Inhibition is equal to the [$Fluorescence_{plus\ inhibitor}$ - $Fluorescence_{background}$] divided by the [$Fluorescence_{minus\ inhibitor}$ - $Fluorescence_{background}$].

A similar protocol can be used for other expressed and purified pro MMPs using substrates and buffers conditions optimal for the particular MMP, for instance as described in C. Graham Knight *et al.*, (1992) FEBS Lett. 296(3):263-266.

Adamalysin family including for example TNF convertase

The ability of the compounds to inhibit proTNF-α convertase enzyme (TACE) may be assessed using a partially purified, isolated enzyme assay, the enzyme being obtained from the membranes of THP-1 as described by K. M. Mohler *et al.*, (1994) Nature 370:218-220. The

purified enzyme activity and inhibition thereof is determined by incubating the partially purified enzyme in the presence or absence of test compounds using the substrate 4',5'-Dimethoxy-fluoresceinyl Ser.Pro.Leu.Ala.Gln.Ala.Val.Arg.Ser.Ser.Ser.Arg.Cys(4-(3-succinimid-1-yl)-fluorescein)-NH_2 in assay buffer (50mM Tris HCl, pH 7.4 containing 0.1% (w/v) Triton X-100 and 2mM $CaCl_2$), at 26°C for 4 hours. The amount of inhibition is determined as for MMP13 except λex 485nm and λem 538nm were used. The substrate was synthesised as follows. The peptidic part of the substrate was assembled on Fmoc-NH-Rink-MBHA-polystyrene resin either manually or on an automated peptide synthesiser by standard methods involving the use of Fmoc-amino acids and O-benzotriazol-1-yl-N,N,N',N'-tetramethyluronium hexafluorophosphate (HBTU) as coupling agent with at least a 4- or 5-fold excess of Fmoc-amino acid and HBTU. Ser^1 and Pro^2 were double-coupled. The following side chain protection strategy was employed; Ser^1(But), Gln^5(Trityl), $Arg^{8,12}$(Pmc or Pbf), $Ser^{9,10,11}$(Trityl), Cys^{13}(Trityl). Following assembly, the N-terminal Fmoc-protecting group was removed by treating the Fmoc-peptidyl-resin with in DMF. The amino-peptidyl-resin so obtained was acylated by treatment for 1.5-2hr at 70°C with 1.5-2 equivalents of 4',5'-dimethoxy-fluorescein-4(5)-carboxylic acid [Khanna & Ullman, (1980) Anal Biochem. 108:156-161) which had been preactivated with diisopropylcarbodiimide and 1-hydroxybenzotriazole in DMF]. The dimethoxyfluoresceinyl-peptide was then simultaneously deprotected and cleaved from the resin by treatment with trifluoroacetic acid containing 5% each of water and triethylsilane. The dimethoxyfluoresceinyl-peptide was isolated by evaporation, trituration with diethyl ether and filtration. The isolated peptide was reacted with 4-(N-maleimido)-fluorescein in DMF containing diisopropylethylamine, the product purified by RP-HPLC and finally isolated by freeze-drying from aqueous acetic acid. The product was characterised by MALDI-TOF MS and amino acid analysis.

Natural Substrates

The activity of the compounds of the invention as inhibitors of aggrecan degradation may be assayed using methods for example based on the disclosures of E. C. Arner *et al.*, (1998) Osteoarthritis and Cartilage 6:214-228; (1999) Journal of Biological Chemistry, 274 (10), 6594-6601 and the antibodies described therein. The potency of compounds to act as inhibitors against collagenases can be determined as described by T. Cawston and A. Barrett (1979) Anal. Biochem. 99:340-345.

Inhibition of metalloproteinase activity in cell/tissue based activity

Test as an agent to inhibit membrane sheddases such as TNF convertase

The ability of the compounds of this invention to inhibit the cellular processing of TNF-α production may be assessed in THP-1 cells using an ELISA to detect released TNF essentially as described K. M. Mohler *et al.*, (1994) Nature 370:218-220. In a similar fashion the processing or shedding of other membrane molecules such as those described in N. M. Hooper *et al.*, (1997) Biochem. J. 321:265-279 may be tested using appropriate cell lines and with suitable antibodies to detect the shed protein.

Test as an agent to inhibit cell based invasion

The ability of the compound of this invention to inhibit the migration of cells in an invasion assay may be determined as described in A. Albini *et al.*, (1987) Cancer Research 47:3239-3245.

Test as an agent to inhibit whole blood TNF sheddase activity

The ability of the compounds of this invention to inhibit TNF-α production is assessed in a human whole blood assay where LPS is used to stimulate the release of TNF-α. 160μl of heparinized (10Units/ml) human blood obtained from volunteers, was added to the plate and incubated with 20μl of test compound (duplicates), in RPMI1640 + bicarbonate, penicillin, streptomycin, glutamine and 1% DMSO, for 30 min at 37°C in a humidified (5%CO_2/95%air) incubator, prior to addition of 20μl LPS (E. coli. 0111:B4; final concentration 10μg/ml). Each assay includes controls of neat blood incubated with medium alone or LPS (6 wells/plate of each). The plates are then incubated for 6 hours at 37°C (humidified incubator), centrifuged (2000rpm for 10 min; 4°C), plasma harvested (50-100μl) and stored in 96 well plates at -70°C before subsequent analysis for TNF-α concentration by ELISA.

Test as an agent to inhibit in vitro cartilage degradation

The ability of the compounds of this invention to inhibit the degradation of the aggrecan or collagen components of cartilage can be assessed essentially as described by K. M. Bottomley *et al.*, (1997) Biochem J. 323:483-488.

In vivo assessment

Test as an anti-TNF agent

The ability of the compounds of this invention as *in vivo* TNF-α inhibitors is assessed in the rat. Briefly, groups of female Wistar Alderley Park (AP) rats (90-100g) are dosed with compound (5 rats) or drug vehicle (5 rats) by the appropriate route e.g. peroral (p.o.), intraperitoneal (i.p.), subcutaneous (s.c.) 1 hour prior to lipopolysaccharide (LPS) challenge (30μg/rat i.v.). Sixty minutes following LPS challenge rats are anaesthetised and a terminal blood sample taken via the posterior vena cavae. Blood is allowed to clot at room temperature for 2hours and serum samples obtained. These are stored at –20°C for TNF-α ELISA and compound concentration analysis.

Data analysis by dedicated software calculates for each compound/dose:

$$\text{Percent inhibition of TNF-}\alpha = \frac{\text{Mean TNF-}\alpha\text{ (Vehicle control)} - \text{Mean TNF-}\alpha\text{ (Treated)}}{\text{Mean TNF-}\alpha\text{ (Vehicle control)}} \times 100$$

Test as an anti-arthritic agent

Activity of a compound as an anti-arthritic is tested in the collagen-induced arthritis (CIA) as defined by D. E. Trentham *et al.*, (1977) J. Exp. Med. 146,:857. In this model acid soluble native type II collagen causes polyarthritis in rats when administered in Freunds incomplete adjuvant. Similar conditions can be used to induce arthritis in mice and primates.

Pharmaceutical Compositions

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of the formula (1), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined hereinbefore in association with a pharmaceutically-acceptable diluent or carrier.

The composition may be in a form suitable for oral administration, for example as a tablet or capsule, for parenteral injection (including intravenous, subcutaneous, intramuscular, intravascular or infusion) as a sterile solution, suspension or emulsion, for topical administration as an ointment or cream or for rectal administration as a suppository.

In general the above compositions may be prepared in a conventional manner using conventional excipients.

The pharmaceutical compositions of this invention will normally be administered to humans so that, for example, a daily dose of 0.5 to 75 mg/kg body weight (and preferably 0.5 to 30 mg/kg body weight) is received. This daily dose may be given in divided doses as necessary, the precise amount of the compound received and the route of administration depending on the weight, age and sex of the patient being treated and on the particular disease condition being treated according to principles known in the art.

Typically unit dosage forms will contain about 1 mg to 500 mg of a compound of this invention.

Therefore in a further aspect of the present invention there is provided a compound of the formula (1), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined hereinbefore, for use in a method of treatment of a warm-blooded animal such as man by therapy.

Also provided is a compound of the formula (1), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined hereinbefore, for use in a method of treating a disease condition mediated by one or more metalloproteinase enzymes and in particular a disease condition mediated by TNF

Further provided is a compound of the formula (1), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined hereinbefore, for use in a method of treating inflammatory diseases, autoimmune diseases, allergic/atopic diseases, transplant rejection, graft versus host disease, cardiovascular disease, reperfusion injury and malignancy in a warm-blooded animal such as man. In particular a compound of the formula (1), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined hereinbefore, is provided for use in a method of treating rheumatoid arthritis, Crohn's disease and psoriasis, and especially rheumatoid arthritis.

According to an additional aspect of the invention there is provided a compound of the formula (1), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined hereinbefore, for use as a medicament.

Also provided is a compound of the formula (1), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined hereinbefore, for use as a medicament in the treatment of a disease condition mediated by one or more metalloproteinase enzymes and in particular a disease condition mediated by TNF-α.

Further provided is a compound of the formula (1), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined hereinbefore, for use as a medicament in the treatment of inflammatory diseases, autoimmune diseases, allergic/atopic diseases, transplant rejection, graft versus host disease, cardiovascular disease, reperfusion injury and malignancy in a warm-blooded animal such as man. In particular a compound of the formula (1), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined hereinbefore, is provided for use as a medicament in the treatment of rheumatoid arthritis, Crohn's disease and psoriasis, and especially rheumatoid arthritis.

According to this another aspect of the invention there is provided the use of a compound of the formula (1), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined hereinbefore in the manufacture of a medicament for use in the treatment of a disease condition mediated by one or more metalloproteinase enzymes and in particular a disease condition mediated by TNF-α in a warm-blooded animal such as man.

Also provided is the use of a compound of the formula (1), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined hereinbefore in the manufacture of a medicament for use in the treatment of inflammatory diseases, autoimmune diseases, allergic/atopic diseases, transplant rejection, graft versus host disease, cardiovascular disease, reperfusion injury and malignancy in a warm-blooded animal such as man. In particular the use of a compound of the formula (1), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined hereinbefore, is provided in the manufacture of a medicament in the treatment of rheumatoid arthritis, Crohn's disease and psoriasis, and especially rheumatoid arthritis.

According to a further feature of this aspect of the invention there is provided a method of producing a metalloprotienase inhibitory effect in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (1).

According to a further feature of this aspect of the invention there is provided a method of producing a TACE inhibitory effect in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (1).

According to this further feature of this aspect of the invention there is provided a method of treating autoimmune disease, allergic/atopic diseases, transplant rejection, graft versus host disease, cardiovascular disease, reperfusion injury and malignancy in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (1).

Also provided is a method of treating rheumatoid arthritis, Crohn's disease and psoriasis, and especially rheumatoid arthritis in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (1).

In addition to their use in therapeutic medicine, the compounds of formula (1) and their pharmaceutically acceptable salts are also useful as pharmacological tools in the development and standardisation of *in vitro* and *in vivo* test systems for the evaluation of the effects of inhibitors of cell cycle activity in laboratory animals such as cats, dogs, rabbits, monkeys, rats and mice, as part of the search for new therapeutic agents.

In the above other pharmaceutical composition, process, method, use and medicament manufacture features, the alternative and preferred embodiments of the compounds of the invention described herein also apply.

The compounds of this invention may be used in combination with other drugs and therapies used in the treatment of various immunological, inflammatory or malignant disease states which would benefit from the inhibition of TACE.

If formulated as a fixed dose such combination products employ the compounds of this invention within the dosage range described herein and the other pharmaceutically-active agent within its approved dosage range. Sequential use is contemplated when a combination formulation is inappropriate.

Examples

The invention will now be illustrated by the following non-limiting examples in which, unless stated otherwise:

(i) temperatures are given in degrees Celsius (°C); operations were carried out at room or ambient temperature, that is, at a temperature in the range of 18-25°C;

(ii) organic solutions were dried over anhydrous magnesium sulphate; evaporation of solvent was carried out using a rotary evaporator under reduced pressure (600-4000 Pascals; 4.5-30 mm Hg) with a bath temperature of up to 60°C;

(iii) chromatography unless otherwise stated means flash chromatography on silica gel; thin layer chromatography (TLC) was carried out on silica gel plates; where a "Bond Elut" column is referred to, this means a column containing 10g or 20g of silica of 40 micron particle size, the silica being contained in a 60ml disposable syringe and supported by a porous disc, obtained from Varian, Harbor City, California, USA under the name "Mega Bond Elut SI". Where an "Isolute™ SCX column" is referred to, this means a column containing benzenesulphonic acid (non-endcapped) obtained from International Sorbent Technology Ltd., 1st House, Duffryn Industial Estate, Ystrad Mynach, Hengoed, Mid Clamorgan, UK. Where Flashmaster II is referred to, this means a UV driven automated chromatography unit supplied by Jones;

(iv) in general, the course of reactions was followed by TLC and reaction times are given for illustration only;

(v) yields, when given, are for illustration only and are not necessarily those which can be obtained by diligent process development; preparations were repeated if more material was required;

(vi) when given, ^{1}H NMR data is quoted and is in the form of delta values for major diagnostic protons, given in parts per million (ppm) relative to tetramethylsilane (TMS) as an internal standard, determined at 400 MHz using $CDCl_3$ as the solvent unless otherwise stated; coupling constants (J) are given in Hz;

(vii) chemical symbols have their usual meanings; SI units and symbols are used;

(viii) solvent ratios are given in percentage by volume;

(ix) mass spectra (MS) were run with an electron energy of 70 electron volts in the chemical ionisation (APCI) mode using a direct exposure probe; where indicated ionisation was effected by electrospray (ES); where values for m/z are given, generally only ions which indicate the parent mass are reported, and unless otherwise stated the mass ion quoted is the positive mass ion - $(M+H)^+$;

(x) LCMS characterisation was performed using a pair of Gilson 306 pumps with Gilson 233 XL sampler and Waters ZMD4000 mass spectrometer. The LC comprised water symmetry 4.6x50 column C18 with 5 micron particle size. The eluents were: A, water with 0.05%

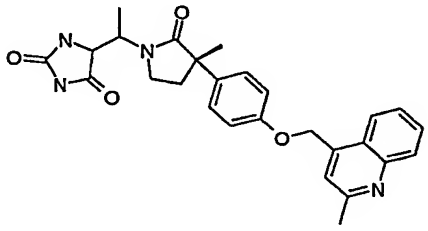
formic acid and B, acetonitrile with 0.05% formic acid. The eluent gradient went from 95% A to 95% B in 6 minutes. Where indicated ionisation was effected by electrospray (ES); where values for m/z are given, generally only ions which indicate the parent mass are reported, and unless otherwise stated the mass ion quoted is the positive mass ion - $(M+H)^+$ and

(xi) the following abbreviations are used:

DMSO	dimethyl sulphoxide;
DMF	*N*-dimethylformamide;
DCM	dichloromethane;
NMP	*N*-methylpyrrolidinone;
DIAD	Di-*iso*propylazodicarboxylate
LHMDS or LiHMDS	Lithium bis(trimethylsilyl)amide
MeOH	Methanol
RT	Room temperature
TFA	Trifluoroacetic acid
EtOH	ethanol
EtOAc	ethyl acetate.
THF	tetrahydrofuran
DIBAL	Di-*iso*butylaluminium hydride

EXAMPLE 1

(R/S)-5-(1-{3-Methyl-3-[4-(2-methyl-quinolin-4-ylmethoxy)-phenyl]-2-oxo-pyrrolidin-1-yl}-ethyl)-imidazolidine-2,4-dione



To a stirred solution of 2-{3-methyl-3-[4-(2-methyl-quinolin-4-ylmethoxy)-phenyl]-2-oxo-pyrrolidin-1-yl}-propionaldehyde (prepared below) (540mg, 1.34mmol) in ethanol (5ml) and water (5ml) was added ammonium carbonate (770mg, 8.0mmol) and potassium cyanide (174mg, 2.68mmol). The mixture was heated to reflux for 1.5 h before addition of a further

portion of ammonium carbonate (300mg, 3.1mmol). Heating was continued for 1h and the solution left to stand at room temperature for 40h. The solution was reheated to reflux for 3h, then evaporated under reduced pressure to give a yellow solid. The residue was partitioned between DCM (30ml) and water (30ml). The aqueous phase extracted with DCM (20ml) and combined organic phases dried (Na_2SO_4) and evaporated. The crude product was purified by chromatography (Flashmaster II, 20g silica bond elute, eluent 2% MeOH / DCM) to give the product, as a mixture of 4 diastereoisomers, as a white foam (200mg, 0.42mmol). MS: 473.

The starting material 2-{3-methyl-3-[4-(2-methyl-quinolin-4-ylmethoxy)-phenyl]-2-oxo-pyrrolidin-1-yl}-propionaldehyde was prepared as follows :

(i) To a solution of **R**-2-[3-(4-hydroxy-phenyl)-3-methyl-2-oxo-pyrrolidin-1-yl]-propionic acid methyl ester§ (725mg, 2.62mmol) in DMSO (30ml) was added 4-chloromethyl-2-methylquinoline† (500mg, 2.62mmol), caesium carbonate (1.7g, 5.2 mmol) and tetra-*n*-butylammonium iodide (1.0g, 2.6 mmol). The resultant solution was stirred at 60 °C for 75 mins. The reaction mixture was allowed to cool then diluted with EtOAc (200ml) and washed with brine (3x100ml). The organic phase was dried (Na_2SO_4), evaporated and purified by chromatography (Flashmaster II, 50g silica bond elute, eluent 50→100% EtOAc / isohexane) to give **R**-2-{3-methyl-3-[4-(2-methyl-quinolin-4-ylmethoxy)-phenyl]-2-oxo-pyrrolidin-1-yl}-propionic acid methyl ester (780mg, 1.8mmol) as an oil. NMR: 1.43 (d, 3H), 1.55 (s, 3H), 2.21 (m, 1H), 2.41 (m, 1H), 2.75 (s, 3H), 3.31 (m, 1H), 3.45 (m, 1H), 3.74 (s, 3H), 4.93 (q, 1H), 5.48 (s, 2H), 6.99 (d, 2H), 7.36 (d, 2H), 7.45 (s, 1H), 7.52 (m, 1H), 7.71 (m, 1H), 7.92 (d, 1H), 8.07 (d, 1H); MS 433.

(ii) **R**-2-{3-Methyl-3-[4-(2-methyl-quinolin-4-ylmethoxy)-phenyl]-2-oxo-pyrrolidin-1-yl}-propionic acid methyl ester (780mg, 1.8mmol) was azeotroped with toluene and dissolved in DCM (10ml) and the solution cooled to –78°C. To this was added a solution of DIBAL (1.0M in DCM, 3.6mmol, 3.6ml) dropwise over 10 mins. The solution was stirred at –78°C for 2h, before quenching with saturated ammonium chloride solution and allowing to warm to room temperature. The solution was then diluted with water (20ml) and DCM (20ml) and the aqueous

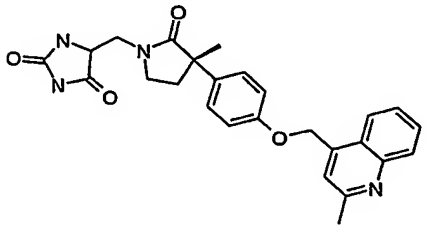
phase extracted with DCM (3x30ml). The combined organic layers were dried (Na_2SO_4), concentrated and purified by chromatography (Flashmaster II, 20g silica bond elute, eluent 50→100% EtOAc / isohexane) to give 2-{3-methyl-3-[4-(2-methyl-quinolin-4-ylmethoxy)-phenyl]-2-oxo-pyrrolidin-1-yl}-propionaldehyde as a 2:1 mixture of diastereoisomers (540mg, 1.34mmol). NMR: 1.37 (d, 3H, major isomer), 1.40 (d, 3H, minor isomer), 1.56(s, 3H, minor isomer), 1.59(s, 3H, major isomer), 2.22-2.28 (m, 1H), 2.45-2.51(m, 1H), 2.75(s, 3H), 3.26-3.36 (m, 2H), 4.71 (q, 1H), 5.49 (s, 2H), 7.00 (d, 2H, minor isomer), 7.01 (d, 2H, major isomer), 7.36 (d, 2H, major isomer), 7.40 (d, 2H, minor isomer), 7.45 (s, 1H), 7.53 (m, 1H), 7.71 (m, 1H), 7.92 (d, 1H), 8.07 (d, 1H); MS: 403.

§ The synthesis of this starting material has been described in WO9918974 and has CAS Registry number 223406-12-0.

† The synthesis of the 4-chloromethyl-2-methylquinoline has been described in WO9965867 and has CAS Registry number 288399-19-9.

EXAMPLE 2

(R/S)-5-{3-Methyl-3-[4-(2-methyl-quinolin-4-ylmethoxy)-phenyl]-2-oxo-pyrrolidin-1-ylmethyl}-imidazolidine-2,4-dione



To a stirred solution of {3-methyl-3-[4-(2-methyl-quinolin-4-ylmethoxy)-phenyl]-2-oxo-pyrrolidin-1-yl}-acetaldehyde (prepared below) (450mg, 1.16mmol) in ethanol (5ml) and water (5ml) was added ammonium carbonate (668mg, 7.0mmol) and potassium cyanide (151mg, 2.3mmol). The mixture was heated to reflux for 3 h before addition of a further portion of ammonium carbonate (300mg, 3.1mmol). Heating was continued for 1 h and the solution allowed to cool and evaporated. The residue was partitioned between DCM (30ml)

and water (30ml). The aqueous phase extracted with DCM (30ml) and combined organic phases dried (Na_2SO_4) and evaporated. The crude product was purified by chromatography (Flashmaster II, 20g silica bond elute, eluent 2%→5% MeOH in DCM) to give the product, as a mixture of 2 diasteoisomers, as a white foam (130mg, 0.28mmol). MS: 457.

The starting material {3-Methyl-3-[4-(2-methyl-quinolin-4-ylmethoxy)-phenyl]-2-oxo-pyrrolidin-1-yl}-acetaldehyde was prepared as follows :

(i) To a solution of 2-(4-benzyloxy-phenyl)-2-methyl-4-oxo-butyric acid methyl ester‡ (3.71g, 11.9mmol) in 1,2-dichloroethane was added glycine methyl ester hydrochloride (1.6g, 12.7mmol) and diisopropylethylamine (2.3ml, 13.2 mmol). The resultant solution was stirred at room temperature for 90 min before addition of sodium triacetoxyborohydride (3.3g, 15.5mmol). The reaction mixture was stirred for a further 2h, before addition of DCM (150ml) and brine (150ml). The aqueous phase was extracted with DCM (150ml). The combined organic phases were dried (Na_2SO_4) and evaporated. The resultant oil was dissolved in toluene (50ml) and heated to 90°C for 1 h, allowed to cool, evaporated and purified by chromatography (Flashmaster II, 100g silica bond elute, eluent 20% EtOAc / isohexane) to give [3-(4-benzyloxy-phenyl)-3-methyl-2-oxo-pyrrolidin-1-yl]-acetic acid methyl ester (2.18g, 6.2 mmol) as a white solid. NMR: 1.55 (s, 3H), 2.19 (m, 1H), 2.43 (m, 1H), 3.41 (m, 2H), 3.73 (s, 3H), 4.13 (s, 2H), 5.04 (s, 2H), 6.93 (d, 2H) 7.29-7.43 (m, 7H); MS 354.

(ii) To a solution of [3-(4-benzyloxy-phenyl)-3-methyl-2-oxo-pyrrolidin-1-yl]-acetic acid methyl ester (2.18g, 6.2 mmol) in ethanol (50ml) was added cyclohexene (6.3 ml, 62mmol) and 10% Pd/C (1.0g). The reaction mixture was heated under reflux for 1h. The reaction mixture was allowed to cool and evaporated to give [3-(4-hydroxy-phenyl)-3-methyl-2-oxo-pyrrolidin-1-yl]-acetic acid methyl ester as an oil (1.6g, 60.8mmol). NMR 1.55(s,3H), 2.19 (m, 1H), 2.42 (m, 1H), 3.44 (m, 2H), 3.74 (s, 3H), 4.13 (s, 2H), 6.74 (d, 2H), 7.24 (d, 2H). MS 264.

(iii) To a solution of [3-(4-hydroxy-phenyl)-3-methyl-2-oxo-pyrrolidin-1-yl]-acetic acid methyl ester (1.0g, 3.8mmol) in DMSO (30ml) was added 4-chloromethyl-2-

methylquinoline† (725mg, 3.8mmol), caesium carbonate (2.48g, 7.6 mmol) and tetra-*n*-butylammonium iodide (1.4g, 3.8 mmol). The resultant solution was stirred at 60 °C for 90 min. The reaction mixture was allowed to cool then diluted with EtOAc (200ml) and washed with brine (3 x 100ml). The organic phase was dried (Na_2SO_4), evaporated and purified by chromatography (Flashmaster II, 50g silica bond elute, eluent 50→100% EtOAc / isohexane) to give {3-Methyl-3-[4-(2-methyl-quinolin-4-ylmethoxy)-phenyl]-2-oxo-pyrrolidin-1-yl}-acetic acid methyl ester (1.0g, 2.4mmol) as an oil. NMR: 1.57 (s, 3H), 2.21 (m, 1H), 2.44 (m, 1H), 2.75 (s, 3H), 3.44 (m, 2H), 3.74 (s, 3H), 4.15 (s, 2H), 5.49 (s, 2H), 7.00 (d, 2H), 7.39 (d, 2H), 7.47 (s, 1H), 7.53 (m, 1H), 7.71 (m, 1H), 7.92 (d, 1H), 8.07 (d, 1H); MS 419.

(iv) {3-Methyl-3-[4-(2-methyl-quinolin-4-ylmethoxy)-phenyl]-2-oxo-pyrrolidin-1-yl}-acetic acid methyl ester (500mg, 1.16mmol) was azeotroped with toluene and dissolved in DCM (6ml) and the solution cooled to –78°C. To this was added a solution of DIBAL (1.0M in DCM, 2.3mmol, 2.3ml) dropwise over 10 minutes. The solution was stirred at –78°C for 1 h, before quenching with saturated ammonium chloride solution and allowing to warm to room temperature. The solution was then diluted with water (10ml) and DCM (10ml) and the aqueous phase extracted with DCM (3x30ml). The organic phase was dried (Na_2SO_4), and evaporated to give the crude aldehyde which was used without further purification. MS: 489.

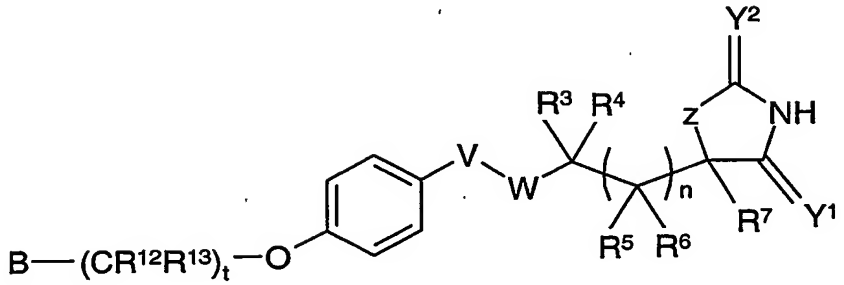
‡ The synthesis of this starting material has been described in WO9918974 and has CAS Registry number 223406-00-6.

† The synthesis of the 4-chloromethyl-2-methylquinoline has been described in WO9965867 and has CAS Registry number 288399-19-9.

CLAIMS

We claim:

1. A compound of formula (1), a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof:



formula (1)

wherein:

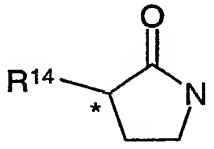
Y^1 and Y^2 are independently O or S;

z is NR^8, O or S;

n is 0 or 1;

W is NR^1, CR^1R^2 or a bond;

V is C(=O), $NR^{15}C(=O)$, $NR^{15}SO_2$, SO_2 or a group of formula (A):



formula (A)

where the group of formula (A) is bonded through nitrogen to W of formula (1) and through carbon * to phenyl of formula (1);

t is 0 or 1;

B is a group selected from aryl, heteroaryl and heterocyclyl where each group is optionally substituted by one or more groups independently selected from nitro, trifluoromethyl, trifluoromethoxy, halo, cyano, C_{1-4}alkyl (optionally substituted by R^9 or one or more halo), C_{2-4}alkenyl (optionally substituted by halo or R^9), C_{2-4}alkynyl (optionally substituted by halo or R^9), C_{3-6}cycloalkyl (optionally substituted by R^9 or one or more halo), C_{5-6}cycloalkenyl (optionally substituted by halo or R^9), aryl (optionally substituted by halo or C_{1-4}alkyl), heteroaryl (optionally substituted by halo or C_{1-4}alkyl), heterocyclyl (optionally substituted by C_{1-4}alkyl), $-SR^{11}$, $-SOR^{11}$, $-SO_2R^{11}$, $-SO_2NR^9R^{10}$, $-NR^9SO_2R^{11}$, $-NHCONR^9R^{10}$, $-OR^9$, $-NR^9R^{10}$, $-CONR^9R^{10}$ and $-NR^9COR^{10}$; or B is C_{2-4}alkenyl or C_{2-4}alkynyl, each being optionally substituted by a group selected from C_{1-4}alkyl, C_{3-6}cycloalkyl, aryl, heteroaryl, heterocyclyl whereby this group is optionally substituted by one or more halo, nitro, cyano, trifluoromethyl, trifluoromethoxy, $-CONHR^9$, $-CONR^9R^{10}$, $-SO_2R^{11}$, $-SO_2NR^9R^{10}$, $-NR^9SO_2R^{11}$, C_{1-4}alkyl and C_{1-4}alkoxy; with the provisos that:

when V is a group of formula (A), C(=O), $NR^{15}C(=O)$ or $NR^{15}SO_2$; or when V is SO_2 and n is 1 and W is NR^1, CR^1R^2 or a bond; or when V is SO_2 and n is 0 and W is CR^1R^2; then B is a group selected from aryl, heteroaryl and heterocyclyl where each group is optionally substituted by one or more groups independently selected from nitro, trifluoromethyl, trifluoromethoxy, halo, cyano, C_{1-4}alkyl (optionally substituted by R^9 or one or more halo), C_{2-4}alkenyl (optionally substituted by halo or R^9), C_{2-4}alkynyl (optionally substituted by halo or R^9), C_{3-6}cycloalkyl (optionally substituted by R^9 or one or more halo), C_{5-6}cycloalkenyl (optionally substituted by halo or R^9), aryl (optionally substituted by halo or C_{1-4}alkyl), heteroaryl (optionally substituted by halo or C_{1-4}alkyl), heterocyclyl (optionally substituted by C_{1-4}alkyl), $-SR^{11}$, $-SOR^{11}$, $-SO_2R^{11}$, $-SO_2NR^9R^{10}$, $-NR^9SO_2R^{11}$, $-NHCONR^9R^{10}$, $-OR^9$, $-NR^9R^{10}$, $-CONR^9R^{10}$ and $-NR^9COR^{10}$; or B is C_{2-4}alkenyl or C_{2-4}alkynyl, each being optionally substituted by a group selected from C_{1-4}alkyl, C_{3-6}cycloalkyl, aryl, heteroaryl, heterocyclyl whereby this group is optionally substituted by one or more halo, nitro, cyano, trifluoromethyl, trifluoromethoxy, $-CONHR^9$, $-CONR^9R^{10}$, $-SO_2R^{11}$, $-SO_2NR^9R^{10}$, $-NR^9SO_2R^{11}$, C_{1-4}alkyl and C_{1-4}alkoxy; and

when V is SO_2 and n is 0 and W is NR^1 or a bond ; then B is a group selected from bicyclic aryl , bicyclic heteroaryl and bicyclic heterocyclyl, where each group is optionally substituted by one or more groups independently selected from nitro, trifluoromethyl, trifluoromethoxy,

halo, cyano, C_{1-4}alkyl (optionally substituted by R^9 or one or more halo), C_{2-4}alkenyl (optionally substituted by halo or R^9), C_{2-4}alkynyl (optionally substituted by halo or R^9), C_{3-6}cycloalkyl (optionally substituted by R^9 or one or more halo), C_{5-6}cycloalkenyl (optionally substituted by halo or R^9), aryl (optionally substituted by halo or C_{1-4}alkyl), heteroaryl (optionally substituted by halo or C_{1-4}alkyl), heterocyclyl (optionally substituted by C_{1-4}alkyl), $-SR^{11}$, $-SOR^{11}$, $-SO_2R^{11}$, $-SO_2NR^9R^{10}$, $-NR^9SO_2R^{11}$, $-NHCONR^9R^{10}$, $-OR^9$, $-NR^9R^{10}$, $-CONR^9R^{10}$ and $-NR^9COR^{10}$; or B is C_{2-4}alkenyl or C_{2-4}alkynyl, each being optionally substituted by a group selected from C_{1-4}alkyl, C_{3-6}cycloalkyl, aryl, heteroaryl, heterocyclyl whereby this group is optionally substituted by one or more halo, nitro, cyano, trifluoromethyl, trifluoromethoxy, $-CONHR^9$, $-CONR^9R^{10}$, $-SO_2R^{11}$, $-SO_2NR^9R^{10}$, $-NR^9SO_2R^{11}$, C_{1-4}alkyl and C_{1-4}alkoxy;

R^1 and R^2 are independently hydrogen or a group selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl and C_{5-6}cycloalkenyl where the group may be optionally substituted by halo, cyano, nitro, hydroxy or C_{1-4}alkoxy;

R^3, R^4, R^5 and R^6 are independently hydrogen or a group selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{5-6}cycloalkenyl, aryl, heteroaryl and heterocyclyl where the group is optionally substituted by one or more substituents independently selected from halo, nitro, cyano, trifluoromethyl, trifluoromethyloxy, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{3-6}cycloalkyl (optionally substituted by one or more R^{17}), aryl (optionally substituted by one or more R^{17}), heteroaryl (optionally substituted by one or more R^{17}), heterocyclyl, $-OR^{18}$, $-SR^{19}$, $-SOR^{19}$, $-SO_2R^{19}$, $-COR^{19}$, $-CO_2R^{18}$, $-CONR^{18}R^{20}$, $-NR^{16}COR^{18}$, $-SO_2NR^{18}R^{20}$ and $-NR^{16}SO_2R^{19}$;

or R^1 and R^3 together with the nitrogen or carbon and carbon to which they are respectively attached form a saturated 3-7-membered ring optionally containing 1 or 2 heteroatoms groups selected from NH, O, S, SO and SO_2 where the ring is optionally substituted on carbon or nitrogen by one or more C_{1-4}alkyl;

or R^3 and R^4 together form a saturated 3- to 7-membered ring optionally containing a heteroatom group selected from NH, O, S, SO and SO_2 where the ring is optionally substituted on carbon or nitrogen by one or more C_{1-4}alkyl;

or R^3 and R^5 together with the carbon atoms to which they are attached form a saturated 3- to 7-membered ring optionally containing a heteroatom group selected from NH, O, S, SO and SO_2 where the ring is optionally substituted on carbon or nitrogen by one or more C_{1-4}alkyl;

or R^5 and R^6 togetherform a saturated 3- to 7-membered ring optionally containing a heteroatom group selected from NH, O, S, SO and SO_2 where the ring is optionally substituted on carbon or nitrogen by one or more C_{1-4}alkyl;

R^7 is hydrogen or a group selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, heteroalkyl, C_{3-7}cycloalkyl, aryl, heteroaryl or heterocyclyl where the group is optionally substituted by halo, C_{1-4}alkyl, C_{1-4}alkoxy, C_{3-7}cycloalkyl, heterocyclyl, aryl, heteroaryl and heteroalkyl; and wherein the group from which R^7 may be selected is optionally substituted on the group and/or on its optional substituent by one or more substitutents independently selected from halo, cyano, C_{1-4}alkyl, nitro, haloC_{1-4}alkyl, heteroalkyl, aryl, heteroaryl, hydroxyC_{1-4}alkyl, C_{3-7}cycloalkyl, heterocyclyl, C_{1-4}alkoxyC_{1-4}alkyl, haloC_{1-4}alkoxyC_{1-4}alkyl, carboxyC_{1-4}alkyl, $-OR^{21}$, $-CO_2R^{21}$, $-SR^{25}$, $-SOR^{25}$, $-SO_2R^{25}$, $-NR^{21}COR^{22}$, $-CONR^{21}R^{22}$ and $-NHCONR^{21}R^{22}$;

or R^3 and R^7 together with the carbon atoms to which they are each attached and $(CR^5R^6)_n$ form a saturated 5- to 7-membered ring optionally containing a heteroatom group selected from NH, O, S, SO and SO_2 where the ring is optionally substituted on carbon or nitrogen by one or more C_{1-4}alkyl;

R^8 is selected from hydrogen, C_{1-6}alkyl and haloC_{1-6}alkyl;

R^9 and R^{10} are independently hydrogen, C_{1-6}alkyl or C_{3-6}cycloalkyl;

or R^9 and R^{10} together with the nitrogen to which they are attached form a heterocyclic 4 to 7-membered ring;

R^{11} is C_{1-6}alkyl or C_{3-6}cycloalkyl;

R^{12} and R^{13} are independently selected from hydrogen, C_{1-6}alkyl and C_{3-6}cycloalkyl;

R^{14} is hydrogen, $-NR^{23}R^{24}$ or C_{1-4}alkyl (optionally substituted by halo, $-OR^{23}$ and $-NR^{23}R^{24}$);
R^{16}, R^{23} and R^{24} are independently hydrogen or C_{1-6}alkyl;

R^{17} is selected from halo, C_{1-6}alkyl, C_{3-6}cycloalkyl and C_{1-6}alkoxy;

R^{18} is hydrogen or a group selected from C_{1-6}alkyl, C_{3-6}cycloalkyl, C_{5-6}cycloalkenyl, saturated heterocyclyl, aryl, heteroaryl, arylC_{1-4}alkyl and heteroarylC_{1-4}alkyl where the group is optionally substituted by one or more halo;

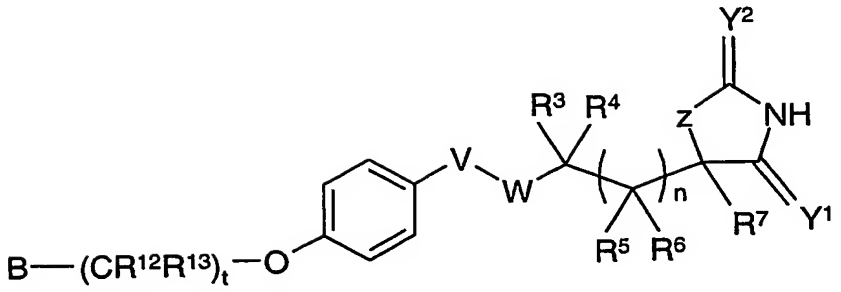
R^{19} and R^{25} are independently a group selected from C_{1-6}alkyl, C_{3-6}cycloalkyl, C_{5-6}cycloalkenyl, saturated heterocyclyl, aryl, heteroaryl, arylC_{1-4}alkyl and heteroarylC_{1-4}alkyl where the group is optionally substituted by one or more halo;

R^{20} is hydrogen, C_{1-6}alkyl or C_{3-6}cycloalkyl;

or R^{18} and R^{20} together with the nitrogen to which they are attached form a heterocyclic 4- to 7- membered ring;

R^{21} and R^{22} are independently hydrogen, C_{1-4}alkyl, haloC_{1-4}alkyl, aryl, arylC_{1-4}alkyl and benzoyl.

2. A compound of formula (1), a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof:



formula (1)

wherein:

Y^1 and Y^2 are independently O or S;

z is NR^8, O or S;

n is 0;

W is NR^1 or a bond;

V is SO_2;

t is 0 or 1;

B is a group selected from aryl, heteroaryl and heterocyclyl where each group is optionally substituted by one or more groups independently selected from nitro, trifluoromethyl, trifluoromethoxy, halo, cyano, C_{1-4}alkyl (optionally substituted by R^9 or one or more halo), C_{2-4}alkenyl (optionally substituted by halo or R^9), C_{2-4}alkynyl (optionally substituted by halo or R^9), C_{3-6}cycloalkyl (optionally substituted by R^9 or one or more halo), C_{5-6}cycloalkenyl (optionally substituted by halo or R^9), aryl (optionally substituted by halo or C_{1-4}alkyl), heteroaryl (optionally substituted by halo or C_{1-4}alkyl), heterocyclyl (optionally substituted by C_{1-4}alkyl), $-SR^9$, $-SOR^{11}$, $-SO_2R^9$, $-SO_2NR^9R^{10}$, $-NR^9SO_2R^{11}$, $-NHCONR^9R^{10}$, $-OR^9$, $-CONR^9R^{10}$ and $-NR^9COR^{10}$; or B is C_{2-4}alkenyl or C_{2-4}alkynyl, each being optionally substituted by a group selected from C_{1-4}alkyl, C_{3-6}cycloalkyl, aryl, heteroaryl, heterocyclyl whereby this group is optionally substituted by one or more halo, nitro, cyano, trifluoromethyl,

trifluoromethoxy, $-CONHR^9$, $-CONR^9R^{10}$, $-SO_2R^{11}$, $-SO_2NR^9R^{10}$, $-NR^9SO_2R^{11}$, C_{1-4}alkyl and C_{1-4}alkoxy;

provided that when t is 0 and B is monocyclic aryl, monocyclic heteroaryl or monocyclic heterocyclyl then the monocyclic group that is B is substituted on the carbon or nitrogen adjacent to the atom to which the oxygen is attached, by a group described above;

R^1 is hydrogen or a group selected from C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{3-5}cycloalkyl and cyclopentenyl where the group may be optionally substituted by halo, cyano, nitro, hydroxy or C_{1-4}alkoxy;

R^3 and R^4 are independently hydrogen or a group selected from C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{3-4}cycloalkyl, cyclopentenyl, aryl, heteroaryl and heterocyclyl where the group is optionally substituted by one or more substituents independently selected from halo, nitro, cyano, trifluoromethyl, trifluoromethyloxy, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{3-6}cycloalkyl (optionally substituted by one or more R^{17}), aryl (optionally substituted by one or more R^{17}), heteroaryl (optionally substituted by one or more R^{17}), heterocyclyl, $-OR^{18}$, $-SR^{19}$, $-SOR^{19}$, $-SO_2R^{19}$, $-CONR^{18}R^{20}$ and $-NR^{16}COR^{18}$;

or R^1 and R^3 together with the nitrogen or carbon and carbon to which they are respectively attached form a saturated 3-7-membered ring optionally containing 1 or 2 heteroatoms groups selected form NH, O, S, SO and SO_2 where the ring is optionally substituted on carbon or nitrogen by one or more C_{1-4}alkyl;

or R^3 and R^4 together form a saturated 3- to 7-membered ring optionally containing a heteroatom group selected from NH, O, S, SO and SO_2 where the ring is optionally substituted on carbon or nitrogen by one or more C_{1-4}alkyl

R^7 is hydrogen or a group selected from C_{1-4}alkyl, heteroalkyl, C_{3-5}cycloalkyl, aryl, heteroaryl or heterocyclyl where the group is optionally substituted by halo, C_{1-4}alkyl, C_{1-4}alkoxy, C_{3-5}cycloalkyl, heterocyclyl, aryl, heteroaryl and heteroalkyl; and wherein the group from which R^7 may be selected is optionally substituted on the group and/or on its optional substituent by one or more substitutents independently selected from halo, cyano, C_{1-4}alkyl, nitro, haloC_{1-}

$_{4}$alkyl, heteroalkyl, aryl, heteroaryl, hydroxyC_{1-4}alkyl, C_{3-5}cycloalkyl, heterocyclyl, C_{1-4}alkoxyC_{1-4}alkyl, haloC_{1-4}alkoxyC_{1-4}alkyl, carboxyC_{1-4}alkyl, $-OR^{21}$, $-CO_2R^{21}$, $-SR^{25}$, $-SOR^{25}$, $-SO_2R^{25}$, $-CONR^{21}R^{22}$ and $-NHCONR^{21}R^{22}$;

or R^3 and R^7 together with the carbon atoms to which they are attached form a saturated 5- to 7-membered ring optionally containing a heteroatom group selected from NH, O, S and SO_2 where the ring is optionally substituted on carbon or nitrogen by one or more C1-4alkyl;

R^8 is selected from hydrogen, C_{1-4}alkyl and haloC_{1-4}alkyl;

R^9 and R^{10} are independently hydrogen, C_{1-4}alkyl or C_{3-5}cycloalkyl;

or R^9 and R^{10} together with the nitrogen to which they are attached form a heterocyclic 4 to 7-membered ring.

R^{11} is C_{1-4}alkyl or C_{3-5}cycloalkyl;

R^{12} and R^{13} are independently selected from hydrogen, C_{1-4}alkyl and C_{3-4}cycloalkyl;

R^{16} is hydrogen or C_{1-4}alkyl;

R^{17} is selected from halo, C_{1-4}alkyl, C_{3-5}cycloalkyl and C_{1-4}alkoxy;

R^{18} is hydrogen or a group selected from C_{1-4}alkyl, C_{3-5}cycloalkyl, C_{5-6}cycloalkenyl, saturated heterocyclyl, aryl, heteroaryl, arylC_{1-4}alkyl and heteroarylC_{1-4}alkyl where the group is optionally substituted by one or more halo;

R^{19} and R^{25} are independently a group selected from C_{1-4}alkyl, C_{3-5}cycloalkyl, C_{5-6}cycloalkenyl, saturated heterocyclyl, aryl, heteroaryl, arylC_{1-4}alkyl and heteroarylC_{1-4}alkyl where the group is optionally substituted by one or more halo;

R^{20} is hydrogen, C_{1-4}alkyl or C_{3-5}cycloalkyl;

or R^{18} and R^{20} together with the nitrogen to which they are attached form a heterocyclic 4- to 6- membered ring;

R^{21} and R^{22} are independently hydrogen, C_{1-4}alkyl, haloC_{1-4}alkyl, aryl, arylC_{1-4}alkyl and benzoyl.

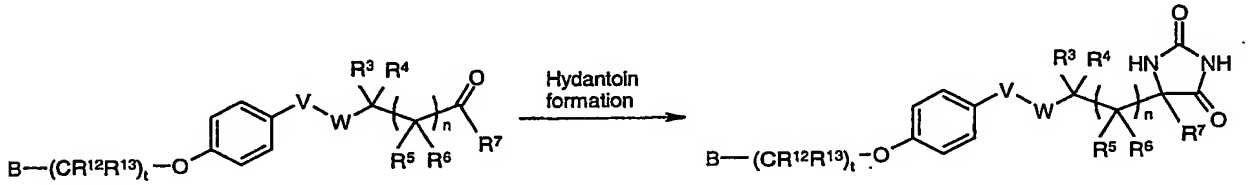
3. A compound according to Claim 1 or Claim 2, for use as a medicament.

4. The use of a compound according to Claim 1 or Claim 2 in the manufacture of a medicament in the treatment of a disease condition mediated by one or more metalloproteinase enzymes.

5. The use of a compound according to Claim 1 or Claim2 in the manufacture of a medicament in the treatment of a disease condition mediated TNF-α.

6. A pharmaceutical composition comprising a compound according to Claim 1 or Claim 2; and a pharmaceutically-acceptable diluent or carrier.

7. A process for preparing a compound according to Claim 1 or Claim 2, comprising the steps of converting a ketone or aldehyde of formula (2) into a compound of formula (1);



formula (2) formula (1)

and thereafter if necessary:

i) converting a compound of the formula (1) into another compound of the formula (1);

ii) removing any protecting groups;

iii) forming a pharmaceutically acceptable salt or *in vivo* hydrolysable ester.